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The National Toxicology Program conducted toxicology and carcinogenesis studies of tetrachloroethylene by inhalation exposure in female F344/N rats and $B_6C_3F_1$ mice. This is a draft report which has not been reviewed and approved by the Peer Review Panel of the National Toxicology Program Board of Scientific Counselors and does not represent the official scientific position of the National Toxicology Program. This draft report summarizes the results of these inhalation carcinogenicity studies.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES

OF

TETRACHLOROETHYLENE
(PERCHLOROETHYLENE)

(CAS NO. 127-18-4)

IN F344/N RATS AND $B6C3F_1$ MICE

(INHALATION STUDIES)

John H. Mennear, Ph.D.
(Chemical Manager)

DRAFT

NATIONAL TOXICOLOGY PROGRAM
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NOTICE

This is NOT a final Technical Report. Until this DRAFT is reviewed and approved by the Peer Review Panel of the NTP Board of Scientific Counselors, this DRAFT does NOT represent the official scientific position of the National Toxicology Program.

NTP TR 311   NIH Publication No. 85-2567

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

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Board Draft, 8/85

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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted in June 1983 for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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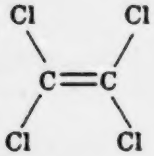

TETRACHLOROETHYLENE
(Perchloroethylene)

(CAS No. 127-18-4)

C_2Cl_4 Molecular Weight: 165.8

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ABSTRACT

Toxicology and carcinogenesis studies of tetrachloroethylene (99.9% pure) were conducted by inhalation exposure of groups of 50 male and 50 female F344/N rats and $B6C3F_1$ mice 6 hours per day, 5 days per week, for 103 weeks. The exposure concentrations used (0, 200, or 400 ppm for rats and 0, 100, or 200 ppm for mice) were selected on the basis of results from 13-week inhalation studies in which groups of 10 rats and 10 mice of each sex were exposed to tetrachloroethylene at 100-1,600 ppm for 6 hours per day, 5 days per week.

During the 13-week studies, 1,600 ppm tetrachloroethylene was lethal to 20%-70% of the rats and mice and reduced the final body weights of survivors. In rats, tetrachloroethylene at 200-800 ppm caused minimal to mild hepatic congestion. In mice, minimal to mild hepatic leukocytic infiltration, centrolobular necrosis, bile stasis (400-1,600 ppm), and mitotic alteration (200-1,600 ppm) were produced in dosed males and females. Tetrachloroethylene exposure also caused renal tubular cell karyomegaly in mice at concentrations as low as 200 ppm.

During the 2-year studies, exposure to tetrachloroethylene did not consistently affect body weight gains in either rats or mice. Exposure at 400 ppm tetrachloroethylene reduced the survival of male rats (vehicle control, 23/50; low dose, 20/50; high dose, 12/50). The reduced male survival may have been related to an increased incidence of mononuclear cell leukemia. Tetrachloroethylene at both exposure concentrations reduced the survival of male mice (46/50, 25/50, 32/50), whereas exposure at 200 ppm reduced female mouse survival (36/50, 31/50, 19/50). Early deaths among mice may have been related to the development of hepatocellular carcinomas.

Both concentrations of tetrachloroethylene were associated with increased incidences of mononuclear cell leukemia in male rats (28/50, 37/50, 37/50; P<0.005). In female rats, the low dose of

tetrachloroethylene increased the incidence of leukemia (18/50, 30/50, 29/50; $P<0.05$) and both concentrations decreased the time to diagnosis of the disease. Tetrachloroethylene produced renal tubular cell karyomegaly in male and female rats and renal tubular cell hyperplasia in male rats. Tetrachloroethylene increased the incidence of renal tubular cell adenomas or adenocarcinomas (combined) in male rats (1/49, 3/49, 4/50). These rare tumors have been consistently found in low incidences in male rats in other 2-year studies of chlorinated ethanes and ethylenes. One low dose male rat had a kidney lipoma and another had a nephroblastoma. Four high dose male and two high dose female rats had gliomas of the brain, whereas one control male and one control female had this tumor.

In male and female mice, tetrachloroethylene caused dose-related increases in the incidences of hepatocellular neoplasms. In males, tetrachloroethylene at 200 ppm increased the incidence of hepatocellular adenomas (11/49, 8/49, 18/50; $P<0.05$) and at both concentrations increased the incidence of hepatocellular carcinomas (7/49, 25/49, 26/50; $P<0.001$). In female mice, tetrachloroethylene at both concentrations increased the incidences of hepatocellular carcinomas (1/48, 13/50, 36/50; $P<0.001$). Tetrachloroethylene also produced renal tubular cell karyomegaly in both sexes of mice, and one low dose male mouse had a tubular cell adenocarcinoma.

In these inhalation studies, there were no neoplastic changes in the respiratory tracts of either species, but there was an increase in the incidence of squamous metaplasia in the nasal cavities in dosed male rats (0/50, 5/50, 5/50).

Tetrachloroethylene was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 in the presence or absence of male Syrian hamster or male Sprague-Dawley rat liver S9. Tetrachloroethylene was not mutagenic in L5178Y/TK$^{+/-}$ mouse lymphoma cells with or without metabolic activation and did not induce sex-linked recessive lethal mutations in Drosophila melanogaster.

An audit of the experimental data was conducted for these carcinogenesis studies on tetrachloroethylene. No data discrepanices were found that influenced the final interpretations.

[illegible]
final report

Under the conditions of these inhalation studies, there was some evidence of carcinogenicity* of tetrachloroethylene in F344/N rats, as shown by increased incidences of mononuclear cell leukemia in males and females and rare renal tubular cell neoplasms in males. There was clear evidence of carcinogenicity in $B6C3F_1$ mice as shown by increased incidences of both hepatocellular adenomas and carcinomas in males and of hepatocellular carcinomas in females.

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*Categories of evidence of carcinogenicity are defined in Note to Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tetrachloroethylene is based on the 13-week studies that began in February 1980 and ended in May 1980 and on the 2-year studies that began in February 1981 and ended in February 1983 at Battelle Pacific Northwest Laboratories.

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I. INTRODUCTION

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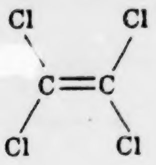

TETRACHLOROETHYLENE
(Perchloroethylene)

(CAS No. 127-18-4)

C_2Cl_4 Molecular Weight: 165.8

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Use, Manufacture, and Occurrence

Tetrachloroethylene is used primarily as a dry cleaning agent, an industrial solvent for fats, oils, tars, rubber, and gums, and a metal degreasing agent (Kirk-Othmer, 1979). Tetrachloroethylene had antihelminthic uses, particularly for hookworms (1.6-8 g/60 kg; Merck, 1976; Kirk-Othmer, 1979; Martindale, 1967), and was formerly used in combination with some grain protectants and fumigants (Farm Chemicals Handbook, 1982).

Tetrachloroethylene has been found in a wide variety of foods in England (McConnell et al., 1975). Individuals living near dry cleaning establishments can be exposed to tetrachloroethylene at concentrations high enough to be measured. For example, the breath of residents living above dry cleaning shops in the Netherlands was found to contain a mean concentration of 5 mg/m^3, and the breath of residents living adjacent to the shops contained 1 mg/m^3 (Verberj and Scheffers, 1979).

In 1983, 547 million pounds of tetrachloroethylene were produced in the United States (USITC, 1984). An estimated 85% of the tetrachloroethylene used annually is lost into the atmosphere (Fuller, 1976). Approximately 500,000 Americans are exposed to this chemical in the workplace (NIOSH, 1978). The present Occupational Safety and Health Administration standard for occupational exposure to tetrachloroethylene in workplace air is a time-weighted average concentration of 50 ppm.

Pharmacokinetics

The major route of human exposure to tetrachloroethylene is via inhalation; however, the chemical is also absorbed after either oral or dermal administration. Absorption through human skin, however, is minimal, and it is unlikely that systemic intoxication can be achieved by this route (Stewart and Dodd, 1964; Riihimaki and Pfaffli, 1978).

Absorption via the lungs is rapid. The exposure concentration has a greater effect on the blood levels achieved than does the duration of the exposure period. In humans, blood levels reach an equilibrium within 3 hours of the initiation of exposure (Hake and Stewart, 1977). Respiratory absorption, as measured by venous blood levels, is increased by exercise (Monster, 1979; Hake and Stewart, 1977).

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Like other lipid soluble materials, tetrachloroethylene is stored in tissues with high lipid content (Stewart, 1969). Savolainen et al. (1977) exposed rats to tetrachloroethylene at a concentration of 200 ppm for 6 hours per day for 4 days and found tetrachloroethylene retained in perirenal fat, brain, and liver tissue. Seventy-two hours after either oral or inhalation exposure of rats and mice to radiolabeled tetrachloroethylene, less than 5% of the administered radioactivity was retained by the body. In rats, most of the retained radioactivity was found in the fat, kidneys, and liver (Pegg et al., 1979; Frantz and Watanabe, 1983; Schumann et al., 1980). In humans, a limited amount of accumulation of tetrachloroethylene, as shown by slightly higher alveolar excretion after each daily exposure (100 ppm, 7.5 hours per day, 5 days per week), was demonstrated by Hake and Stewart (1977).

Tetrachloroethylene, either inhaled or ingested by rats, is excreted primarily through the lungs. Male Sprague-Dawley rats exposed to ^{14}C-tetrachloroethylene by either gavage (1.0 mg/kg) or inhalation (10 ppm) excreted 70% of the dose unchanged in expired air (Pegg et al., 1979). Approximately 3% was excreted as carbon dioxide, and approximately 23% was excreted in the urine and feces as nonvolatile metabolites. When doses were increased to 500 mg/kg and 600 ppm, approximately 89% of the doses was excreted unchanged from the lungs. When 1,000 mg/kg of tetrachloroethylene was administered to Wistar rats by gavage, 89% of the dose was excreted unchanged via the lungs (Daniel, 1963). The results reported by Pegg et al. (1979) are consistent with the hypothesis that the metabolism of tetrachloroethylene in the rat is a saturable process.

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Mice (strain unspecified) that were exposed for 2 hours to radiolabeled tetrachloroethylene at 200 ppm by inhalation excreted 70% of the administered radioactivity in expired air, 20% in the urine, and less

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than 0.5% in feces (Yllner, 1961). When exposed to tetrachloroethylene at lower concentrations (10 ppm for 6 hours), $B6C3F_1$ mice excreted 12% of the dose via the lungs (Schumann et al., 1980).

The major metabolite of tetrachloroethylene found in the urine of rats, mice, and hamsters is trichloroacetic acid (Yllner, 1961; Daniel, 1963; Ikeda and Imamura, 1973; Moslen et al., 1977). Minor metabolites found by these investigators included oxalic acid and ethylene glycol. Pegg et al. (1979), however, found only oxalic acid in the urine of rats administered tetrachloroethylene.

$B6C3F_1$ mice were reported to metabolize tetrachloroethylene to a greater extent than Osborne-Mendel rats. When tetrachloroethylene was inhaled at a concentration of 10 ppm for 6 hours, mice were estimated to metabolize 8.6 times more tetrachloroethylene per unit body weight than did rats (Schumann et al., 1980). When a single oral dose of 500 mg/kg was employed, the differential between the species was reduced to 1.6, with mice metabolizing less of the oral dose than of the inhaled dose.

In humans, trichloro compounds were identified as urinary metabolites of tetrachloroethylene. Urinary trichloroacetic acid was reported to appear in the urine of exposed workers (Weiss, 1969; Ikeda and Ohtsuji, 1972; Ikeda et al., 1972; Ikeda and Imamura, 1973; Münzer and Heder, 1973). Urinary trichloroethanol also was detected as a metabolite in exposed workers (Ikeda and Ohtsuji, 1972; Ikeda et al., 1972). In controlled inhalation experiments in humans (70-200 ppm for 1-8 hours), less than 2% of the absorbed dose was recovered as urinary trichloroacetic acid (Fernandez et al., 1976; Hake and Stewart, 1977; Monster, 1979). Ikeda et al. (1972) found that the trichloroacetic acid content of the urine reaches a plateau after repeated exposures at over 50 ppm. These results are suggestive of a saturable metabolic process for tetrachloroethylene in humans.

Teratogenicity

Tetrachloroethylene was not teratogenic for Swiss Webster mice or Sprague-Dawley rats exposed by inhalation at 300 ppm for 7 hours per day on days 6-15 of gestation (Schwetz et al., 1975). However, the pups of exposed rats exhibited reduced body weights, and there was a slightly increased incidence of resorptions in dosed rats. In mice, tetrachloroethylene administration was associated with reduced weight of pups, delayed ossification of skull bones, increased subcutaneous edema, and split sternebrae. Hardin et al. (1981) exposed pregnant rats and rabbits to tetrachloroethylene at 500 ppm and found no evidence of reproductive toxicity or teratogenic potential.

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Genetic Toxicology

Tetrachloroethylene (99.7% pure) was not mutagenic in strain TA100 of Salmonella in the presence of phenobarbitol-induced rat liver S9 (Bartsch et al., 1979), and tetrachloroethylene was not mutagenic in strain TA1535 in the absence of S9 (Kringstad et al., 1981). Tetrachloroethylene was not mutagenic in four strains of Salmonella in the absence or presence of hamster or rat liver S9 (EMTDP, 1982, Appendix G). Tetrachloroethylene was also not mutagenic in L5178Y/TK$^{+/-}$ mouse lymphoma cells with or without metabolic activation and did not induce sex-linked recessive lethal mutations in Drosophila (Appendix G).

Tetrachloroethylene was reported to induce twofold increases in the reversion frequency in TA100; however, the tetrachloroethylene sample was only 99.0% pure, and the weak positive result may have been due to contaminants (Kringstad et al., 1981). The use of tetrachloroethylene of unknown purity increased the frequency of gene conversion and mitotic recombination in yeast (Callen et al., 1980).

Tetrachloroethylene did not induce chromosomal aberrations in bone marrow cells of mice (Cerna and Kypenova, 1977), but these findings are difficult to evaluate because details of the protocol and results are lacking. Additional studies showed that tetrachloroethylene did not induce chromosomal aberrations or sister-chromatid exchanges (SCE's) in Chinese hamster ovary cells in vitro (Appendix G). These results are consistent with the lack of cytogenetic effects of tetrachloroethylene in humans exposed in the workplace (Ikeda et al., 1980).

In conclusion, tetrachloroethylene appears to be nonmutagenic in bacteria and mouse lymphoma cells and does not cause chromosomal aberrations or SCE's. The few positive findings that tetrachloroethylene was genotoxic may be due to the impurities in the compound tested.

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Carcinogenicity

In an earlier study, administration of tetrachloroethylene in corn oil by gavage produced hepatocellular carcinomas in male and female $B6C3F_1$ mice (males received 450 or 900 mg/kg for 11 weeks, then 550 or 1,100 mg/kg for 67 weeks; females received 300 or 600 mg/kg for 11 weeks, then 400 or 800 mg/kg for 67 weeks) (NCI, 1977). In a simultaneous study in Osborne-Mendel rats, administration of tetrachloroethylene did not produce tumors (males were administered 500 or 1,000 mg/kg and females were administered 700 or 1,400 mg/kg for 78 weeks); however, survival in dosed rats was reduced. These studies were judged inadequate to assess carcinogenic potential in male and female Osborne-Mendel rats.

Exposure of male and female Sprague-Dawley rats to tetrachloroethylene (300 or 600 ppm, 6 hours per day, 5 days per week for 52 weeks) by inhalation did not increase the incidence of tumors in either sex (Rampy et al., 1978). However, the duration of dosing was only 1 year, although the animals were observed for the rest of their lives. Strain A/St mice did not develop an increase in pulmonary tumors after tetrachloroethylene administration (14 intraperitoneal injections of 80 mg/kg, 24 injections of 200 mg/kg, or 48 injections of 400 mg/kg (Theiss et al., 1977).

Tetrachloroethylene did not initiate skin tumors in female ICR/Ha Swiss mice (Van Duuren et al., 1979). The mice received either a single application of 163 mg of tetrachloroethylene followed by topical

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applications of phorbol myristate acetate three times per week until the end of the study (428-576 days) or three weekly applications of 18 or 54 mg of tetrachloroethylene in acetone for 440-594 days.

The International Agency for Research on Cancer (IARC, 1979) concluded that there was limited evidence that tetrachloroethylene was carcinogenic in mice. Because of the early deaths among Osborne-Mendel rats used in the earlier study (NCI, 1977), the rat portion of that study was considered to be inadequate for determining whether tetrachloroethylene caused cancer in rats. Consequently, the NCI initiated additional studies in which four strains of rats (Long-Evans, Sherman, Wistar, and F344/N) and female $B6C3F_1$ mice were to be studied by gavage and F344/N rats and $B6C3F_1$ mice were to be studied by inhalation. The in-life portions of the gavage studies have been completed, and the data are being reviewed. The present report describes the results of the inhalation studies of tetrachloroethylene.

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TETRACHLOROETHYLENE
GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS
SINGLE-EXPOSURE STUDIES
FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
    Study Design
    Source and Specifications of Test Animals
    Animal Maintenance
    Clinical Examinations and Pathology
    Statistical Methods

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PROCUREMENT AND CHARACTERIZATION OF TETRACHLOROETHYLENE

High-purity tetrachloroethylene (Dowper$^{(R)}$ stabilized) was obtained from the Dow Chemical USA in two lots (Table 1). Purity and identity analyses were conducted at Midwest Research Institute (Appendix H).

The identities of both lots were confirmed by spectroscopic analysis. The infrared spectra were consistent with that found in the literature. No peaks were observed in the nuclear magnetic resonance spectra, a finding consistent with the structure of tetrachloroethylene and suggesting the absence of major impurities. The cumulative data from elemental analyses and gas chromatography indicated that the purity of both lots was approximately 99.9%.

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE INHALATION STUDIES OF TETRACHLOROETHYLENE

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
TA03116F-01	TA03116F-01	TA03116F-01	TA08190D
Supplier			
Dow Chemical USA (Midland, MI)	Same as the single-exposure studies	Same as the single-exposure studies	Same as the single-exposure studies

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Tetrachloroethylene requires small quantities of inhibitors to prevent decomposition. The manufacturer stated that the lots used in the current studies contained 53 ppm of N-methylmorpholine. Tetrachloroethylene was found to be stable for 2 weeks at 60° C (Appendix B). Tetrachloroethylene was stored at 0° C. Results of periodic analyses of the bulk chemical at the testing laboratory by infrared spectroscopy and gas chromatography indicated that tetrachloroethylene was stable under these storage conditions.

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

Tetrachloroethylene was vaporized at 100°-110° C, diluted with air, and introduced into the chambers (Table 2 and Appendix I). Concentrations in the exposure chambers were monitored 8-12 times per exposure period by a Hewlett-Packard 5840A Gas Chromatograph. Average weekly exposure concentrations are presented in Appendix I. On one occasion (September 13, 1982) in the 2-year studies, the concentration in the 400-ppm chamber was 800 ppm for 12 minutes and 2,400 ppm for 48 minutes. Animals were therefore not exposed at all on September 14, 1982. A summary and the distribution of the chamber concentrations in the 2-year studies are given in Tables 3 and 4.

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TABLE 2. GENERATION OF CHAMBER CONCENTRATIONS IN THE INHALATION STUDIES OF TETRACHLOROETHYLENE

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Tetrachloroethylene vapor was generated by bubbling clean, dry air (−40° C dewpoint) through all glass impingers that contained tetrachloroethylene; the different concentrations were obtained by varying the amount of air that was passed through the test material.	Same as the single-exposure studies	Tetrachloroethylene was vaporized at 100°-110° C, diluted with air, and introduced into the chamber with a stable micrometering pump with adjustable drift-free pump rates. The vaporizer was heated to 110° ± 3° C. The test material vapor entered the fresh air duct and was led directly into the exposure chamber.	The test material was pumped from a stainless steel reservoir to a vaporizer by a stable micrometering pump

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TABLE 3. SUMMARY OF CHAMBER CONCENTRATIONS OF TETRACHLOROETHYLENE DURING THE TWO-YEAR INHALATION STUDIES

Target Concentration (ppm)	Total Number of Readings	Mean Concentration (a) (ppm)
100	4,666	99.5 ± 6.6
200	4,649	201 ± 11
400	4,643	403 ± 36

(a) Mean ± standard deviation

TABLE 4. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF TETRACHLOROETHYLENE DURING THE TWO-YEAR INHALATION STUDIES

Range of Concentration (percent of target)	Number of Days Mean within the Range		
	100 ppm	200 ppm	400 ppm
>150	0	0	0
130-150	0	0	1
120-130	0	0	0
110-120	1	5	0
100-110	203	260	286
90-100	279	224	200
80-90	7	1	3
70-80	2	2	2

SINGLE-EXPOSURE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and observed for 16 days before being placed on study. The studies were conducted at Industrial Biotest Laboratories.

Groups of five rats of each sex were exposed to air containing tetrachloroethylene at concentrations of 2,445, 3,786, 4,092, 4,513, or 5,163 ppm for 4 hours. Groups of five mice of each sex were exposed at concentrations of 2,328, 2,445, 2,613, 2,971, or 3,786 ppm. Rats and mice were observed daily and weighed on days 0 and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

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TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF TETRACHLOROETHYLENE

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Test Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 male and 50 female rats; 49 or 50 male and female mice
Doses			
Rats--2,445, 3,786, 4,092, 4,513, or 5,163 ppm tetrachloroethylene by inhalation; mice--2,328, 2,445, 2,613, 2,971, or 3,786 ppm tetrachloroethylene by inhalation	Target--0, 100, 200, 425, 875, or 1,750 ppm tetrachloroethylene by inhalation	Target--0, 100, 200, 400, 800, or 1,600 ppm tetrachloroethylene by inhalation	Rats--0, 200, or 400 ppm tetrachloroethylene by inhalation; mice--0, 100, or 200 ppm tetrachloroethylene by inhalation
Date of First Dose			
6/9/77; 6/12/77; 6/13/77; 6/16/77; 6/21/77	10/14/77	2/21/80	2/18/81
Date of Last Dose			
NA	10/27/77	5/21/80	2/4/83
Duration of Dosing			
One 4-h exposure	6 h/d, 5 d/wk for 2 wk (10 exposures)	6 h/d, 5 d/wk for 13 wk	6 h/d, 5 d/wk for 103 wk
Type and Frequency of Observation			
Weighed before and after exposure	Observed 1 × d; weighed on d 0, 5, 10, and 15	Observed continuously during the exposure period, 3 × d on nonexposure days; weighed 1 × wk	Same as 13-wk studies.
Necropsy and Histologic Examination			
Necropsy performed on all animals	Necropsy performed on all animals; the following tissues were examined microscopically: skin, mandibular lymph node, salivary gland, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, colon, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, and pituitary gland	Necropsy on all animals. The following tissues were examined microscopically in the control and high dose groups: skin, mandibular lymph node, mammary gland, salivary gland, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, esophagus, stomach, duodenum, colon, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, and pituitary gland. Rats: 200, 400, 800 ppm--liver; 800 ppm lungs and bronchi; mice: 100 ppm--kidneys; 200, 400, 800 ppm--liver	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, mandibular lymph node, sternebrae including marrow, thyroid gland, parathyroids, small intestine, rectum, colon, liver, mammary gland, prostate/testes or ovaries/uterus, lungs and mainstem bronchi, nasal cavity and nasal turbinates, skin, salivary gland, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, gallbladder (mice), and tracheobronchial lymph nodes

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TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF TETRACHLOROETHYLENE (Continued)

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	Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	Frederick Cancer Research Center	Charles River Breeding Laboratories (Wilmington, MA)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Testing Laboratory	Industrial Biotest Laboratories	Industrial Biotest Laboratories	Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories
Method of Animal Identification	Ear notch	Ear notch	Ear tags	Same as 13-wk studies
Time Held Before Test	7 d	16 d	22 d	21 d
Age When Placed on Study	5-7 wk	6-8 wk	7-9 wk	8-9 wk
Age When Killed	7-9 wk	8-10 wk	20-22 wk	112-113 wk
Necropsy Dates	NA	10/28/77	5/23/80	2/14/83-2/18/83
Method of Animal Distribution	Stratified by weight and then assigned to groups according to a table of random numbers	Same as single-exposure studies	According to computer-generated tables of random numbers	Same as 13-wk studies
Feed	Wayne Lab Blox® (Allied Mills, Chicago, IL); available ad libitum except during inhalation exposures	Same as single-exposure studies	NIH 07 Open Formula (Zeigler Bros.,Gardners, PA); available ad libitum except during inhalation exposures	Same as 13-wk studies
Water	Automatic watering system; provided ad libitum	Same as single-exposure studies	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 13-wk studies
Cages	Stainless steel mesh (Unifab Corp., Kalamazoo, MI)	Same as single-exposure studies	Stainless steel wire	Same as 13-wk studies
Animals per Cage	1	1	1	1

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF TETRACHLOROETHYLENE (Continued)

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Other Chemicals on Test in the Same Room			
Not available	Dichloromethane, d 1-11	Dichloromethane	Dichloromethane
Animal Room Environment			
Not available	Not available	Temp--72°-80° F within exposure chambers, 72°-76° F during exposure period; humidity--40%-80% within exposure chambers, 40%-60% during postexposure period; fluorescent light 12 h/d	Temperature--67°-83° F; humidity range--20%-83%; fluorescent light 12 h/d

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FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 16 days before being placed on study. The animals were 6-8 weeks old when the studies began. The studies were conducted at Industrial Biotest Laboratories.

Groups of five rats and five mice of each sex were exposed to air containing tetrachloroethylene at target concentrations of 0, 100, 200, 425, 875, or 1,750 ppm, 6 hours per day, 5 days per week for 2 weeks (10 exposures). Rats and mice were observed daily and weighed on days 0, 5, 10, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

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THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to tetrachloroethylene and to determine the concentrations to be used in the 2-year studies.

Four- to 6-week-old male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 22 days, and assigned to test groups according to a table of random numbers. Feed was available ad libitum during nonexposure periods, and water was available at all times.

Groups of 10 rats and mice of each sex were exposed to air containing tetrachloroethylene at target concentrations of 0, 100, 200, 400, 800, or 1,600 ppm, 6 hours per day, 5 days per week for 13 weeks.

Animals were checked continually during exposure and three times per day on nonexposure days; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. Tissues and groups examined are listed in Table 5.

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TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were exposed to air containing tetrachloroethylene at concentrations of 0 (chamber control), 200, or 400 ppm, 6 hours per day, 5 days per week for 103 weeks. Groups of 49 or 50 mice of each sex were exposed at concentrations of 0, 100, or 200 ppm on the same schedule.

Source and Specifications of Test Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, x C3H/HeN MTV^-, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the testing laboratory at 5 weeks of age and mice at 5-6 weeks. The animals were quarantined at the testing facility for 21 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 8 weeks of age and mice at 9 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP. Serologic analyses of control animals were performed at the end of the studies (Appendix J).

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A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because matched concurrent controls were included in each study.

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Animal Maintenance

Rats and mice were housed individually. Feed and water were freely available except during exposure periods, when only water was available.

Clinical Examinations and Pathology

All animals were observed two times per day. Clinical signs were recorded at least once per month. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the

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Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group.

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

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Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends.

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For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

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Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for decisionmaking, there are certain instances in which historical control data can be helpful in the overall evaluation of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors in these studies appearing to show compound-related effects.

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III. RESULTS

RATS

- SINGLE-EXPOSURE STUDIES
- FOURTEEN-DAY STUDIES
- THIRTEEN-WEEK STUDIES
- TWO-YEAR STUDIES
  - Body Weights and Clinical Signs
  - Survival
  - Pathology and Statistical Analyses of Results

MICE

- SINGLE-EXPOSURE STUDIES
- FOURTEEN-DAY STUDIES
- THIRTEEN-WEEK STUDIES
- TWO-YEAR STUDIES
  - Body Weights and Clinical Signs
  - Survival
  - Pathology and Statistical Analyses of Results

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RATS

SINGLE-EXPOSURE STUDIES

All the rats that were exposed at 5,163 ppm died before the end of the studies (Table 6). Mean body weight gain was not dose related. Hypoactivity, ataxia, and anesthesia were observed in all dosed groups.

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TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-EXPOSURE INHALATION STUDIES OF TETRACHLOROETHYLENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams)		
		Initial (b)	Final	Change (c)
MALE				
2,445	5/5	87 ± 4	149 ± 4	+ 62 ± 4
3,786	4/5	95 ± 12	166 ± 5	+ 60 ± 3
4,092	3/5	107 ± 4	160 ± 10	+ 51 ± 3
4,513	3/5	124 ± 4	187 ± 5	+ 60 ± 2
5,163	0/5	150 ± 6	(d)	(d)
FEMALE				
2,445	5/5	74 ± 3	107 ± 1	+ 33 ± 3
3,786	1/5	80 ± 2	112	+ 30
4,092	2/5	88 ± 2	116 ± 4	+ 32 ± 1
4,513	2/5	100 ± 2	128 ± 10	+ 26 ± 6
5,163	0/5	109 ± 4	(d)	(d)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) No data are presented due to the 100% mortality in this group.

FOURTEEN-DAY STUDIES

Two of five male rats and 3/5 female rats exposed at 1,750 ppm died before the end of the studies (Table 7). No other deaths occurred. The final mean body weight of male rats exposed at 1,750 ppm was 72% that of the controls. Dyspnea, hypoactivity, and ataxia were observed in rats in the highest dose group.

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TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY INHALATION STUDIES OF TETRACHLOROETHYLENE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	115 ± 3	169 ± 5	+ 54 ± 2	--
100	5/5	118 ± 5	176 ± 7	+ 58 ± 4	104
200	5/5	115 ± 4	163 ± 5	+ 48 ± 2	96
425	5/5	110 ± 2	166 ± 3	+ 56 ± 2	98
875	5/5	112 ± 3	169 ± 3	+ 57 ± 2	100
1,750	(d) 3/5	108 ± 3	122 ± 3	+ 17 ± 1	72
FEMALE					
0	5/5	97 ± 4	124 ± 4	+ 27 ± 1	--
100	5/5	98 ± 3	124 ± 6	+ 26 ± 3	100
200	5/5	97 ± 3	122 ± 5	+ 25 ± 4	98
425	5/5	96 ± 3	121 ± 4	+ 25 ± 3	98
875	5/5	96 ± 3	122 ± 1	+ 26 ± 3	98
1,750	(e) 2/5	94 ± 4	123 ± 5	+ 26 ± 2	104

(a) Number surviving/number in group

(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.

(c) Mean body weight change of the survivors of the group ± standard error of the mean

(d) Days of death: 7, 8

(e) Days of death: 7, 8, 13

THIRTEEN-WEEK STUDIES

Four of 10 male and 7/10 female rats exposed at 1,600 ppm died before the end of the studies (Table 8). Final mean body weights of rats exposed at 1,600 ppm were 20% lower than that of the controls for males and 11% lower for females.

Lung congestion was observed in rats exposed at 1,600 ppm. The incidence and severity of hepatic congestion in rats was dose related (Table 9). Congestion was most severe in animals that died before the end of the studies.

Dose Selection Rationale: Because of the incidence of deaths at 1,600 ppm and the incidence of liver lesions at lower concentrations, exposure concentrations of 200 and 400 ppm tetrachloroethylene were selected for rats for the 2-year studies.

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TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF TETRACHLOROETHYLENE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	194 ± 4	358 ± 6	+ 164 ± 5	–
100	10/10	204 ± 4	352 ± 8	+ 148 ± 8	98
200	10/10	197 ± 5	358 ± 6	+ 161 ± 7	100
400	10/10	200 ± 5	349 ± 8	+ 149 ± 7	97
800	10/10	202 ± 5	350 ± 6	+ 148 ± 7	98
1,600	(d) 6/10	199 ± 5	286 ± 3	+ 80 ± 7	80
FEMALE					
0	10/10	142 ± 3	206 ± 5	+ 64 ± 3	--
100	10/10	137 ± 3	197 ± 3	+ 60 ± 3	96
200	10/10	137 ± 3	202 ± 4	+ 65 ± 3	98
400	10/10	140 ± 3	206 ± 4	+ 66 ± 4	100
800	10/10	141 ± 2	204 ± 2	+ 63 ± 1	99
1,600	(e) 3/10	140 ± 3	183 ± 4	+ 37 ± 1	89

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 1, 11, 13, 13
(e) Week of death: 5, 5, 5, 6, 7, 12, 13

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TABLE 9. SEVERITY OF LIVER OR LUNG CONGESTION IN RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF TETRACHLOROETHYLENE

Group	Liver Male	Liver Female	Lung Male	Lung Female
Control	(a) 1/10 (2.0)	0/9	0/10	0/9
200 ppm	2/10 (2.0)	1/10 (1.0)	--	–
400 ppm	3/10 (1.7)	5/10 (1.8)	--	--
800 ppm	5/10 (1.6)	5/10 (1.6)	0/10	0/10
1,600 ppm	7/10 (2.0)	8/9 (1.8)	7/10 (2.4)	7/10 (3.0)

(a) Incidence of lesion; mean severity score of affected animals is in parentheses: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control groups were comparable throughout the studies (Table 10 and Figure 1).

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TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

Weeks on Study	Control		200 ppm			400 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	162	50	164	101	50	165	102	50
1	182	50	191	105	50	194	107	50
2	212	50	219	103	50	221	104	50
3	234	50	241	103	50	245	105	50
4	255	50	260	102	50	264	104	50
5	274	50	277	101	50	275	100	50
6	284	50	292	103	50	289	102	50
7	295	50	300	102	50	295	100	50
8	308	50	313	102	50	309	100	50
9	309	50	293	95	50	290	94	50
10	316	50	292	92	50	296	93	50
11	329	50	325	99	50	324	98	50
12	333	50	329	99	50	336	101	50
13	341	50	344	101	50	340	100	50
17	367	50	370	101	50	369	101	50
21	396	50	397	100	50	394	99	50
25	418	50	412	99	50	408	98	50
28	424	50	419	99	50	418	99	50
34	425	50	423	100	49	420	99	50
38	431	50	426	99	49	428	99	50
43	447	50	440	98	48	437	98	50
47	452	50	447	99	48	452	100	50
51	460	50	457	99	48	457	99	50
55	468	50	465	99	47	463	99	50
60	471	50	471	100	47	469	100	50
64	477	50	471	99	47	471	99	50
69	483	48	477	99	46	475	98	49
73	486	48	479	99	45	471	97	49
78	484	48	476	98	45	477	99	47
82	484	48	475	98	43	466	96	45
86	480	46	469	98	40	470	98	37
90	471	42	445	94	36	464	99	34
95	456	38	455	100	34	447	98	31
99	448	33	441	98	28	435	97	27
FEMALE								
0	119	50	121	102	50	120	101	50
1	127	50	135	106	50	134	106	50
2	136	50	148	109	50	148	109	50
3	147	50	156	106	50	152	103	50
4	158	50	166	105	50	165	104	50
5	167	50	175	105	50	168	101	50
6	173	50	179	103	50	176	102	50
7	177	50	187	106	50	181	102	50
8	185	50	193	104	50	187	101	50
9	187	50	177	95	50	174	93	50
10	190	50	186	98	50	178	94	50
11	193	50	199	103	50	195	101	50
12	197	50	193	98	50	199	101	50
13	198	50	203	103	50	198	100	50
17	209	50	213	102	50	208	100	50
21	218	50	227	104	50	220	101	50
25	225	50	233	104	50	227	101	50
28	233	50	236	101	50	230	99	50
34	234	50	240	103	50	231	99	50
38	238	50	244	103	50	236	99	50
43	252	50	260	103	50	248	98	50
47	257	50	266	104	50	257	100	50
51	266	50	275	103	50	262	98	50
55	273	50	283	104	50	271	99	50
60	284	49	292	103	50	281	99	50
64	292	48	302	103	49	293	100	50
69	300	48	311	104	49	300	100	50
73	313	47	317	101	48	308	98	50
78	316	47	319	101	46	312	99	48
82	320	47	323	101	44	318	99	43
86	323	43	325	101	41	318	98	39
90	323	38	325	101	39	323	100	36
95	317	36	318	100	35	317	100	34
99	320	30	322	101	28	322	101	32

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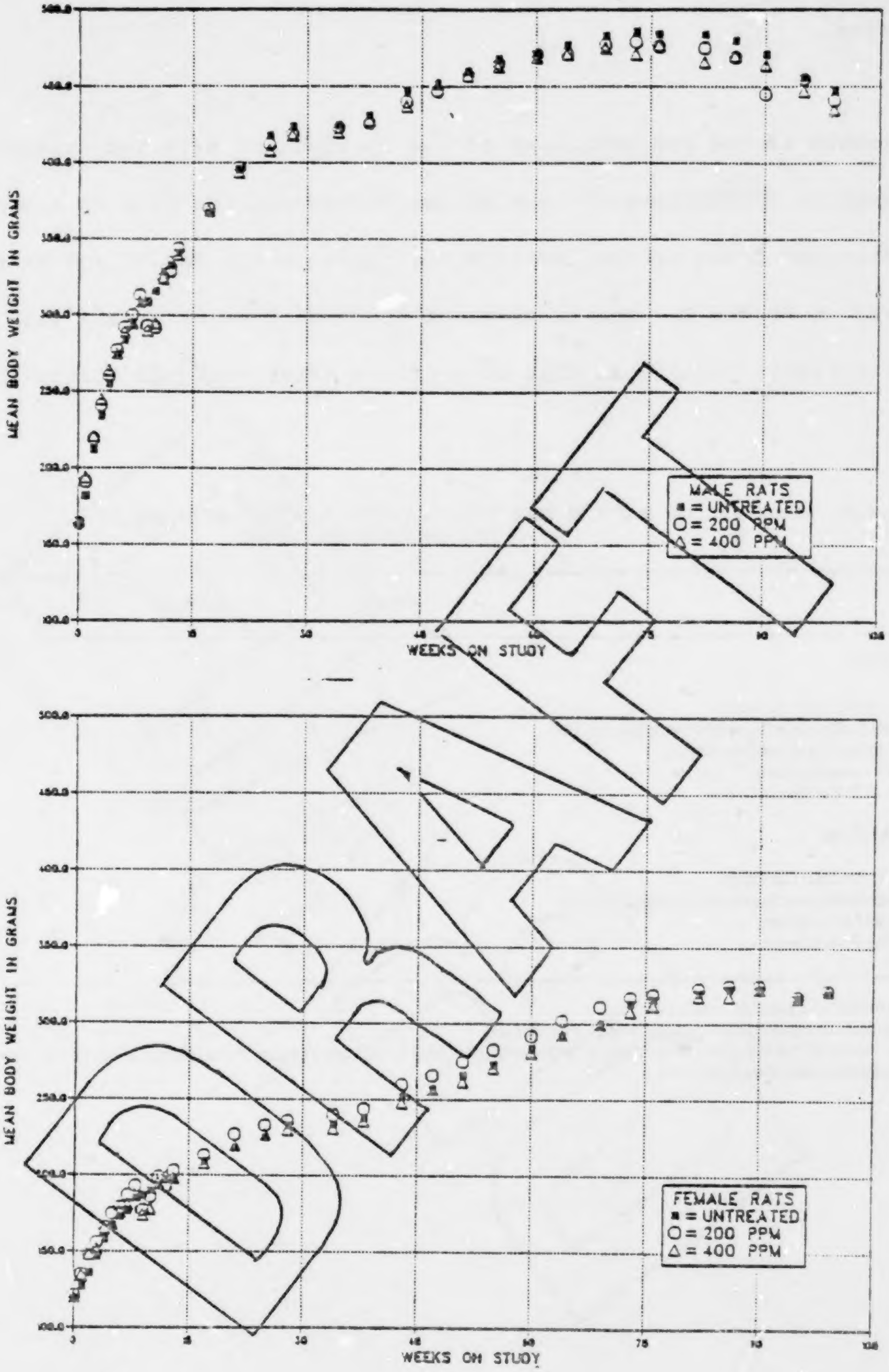

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FIGURE 1. GROWTH CURVES FOR RATS EXPOSED TO TETRACHLOROETHYLENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats exposed to tetrachloroethylene at the concentrations used in these studies and those of the controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the high dose male rats was significantly lower than that of controls after week 102 (Table 11).

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	27	30	38
Died during termination period	0	1	1
Killed at termination	23	19	11
Survival P values (c)	0.024	0.482	0.023
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	27	29	26
Killed at termination	23	21	24
Survival P values (c)	1.000	0.767	0.990

(a) Terminal kill period: week 104

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

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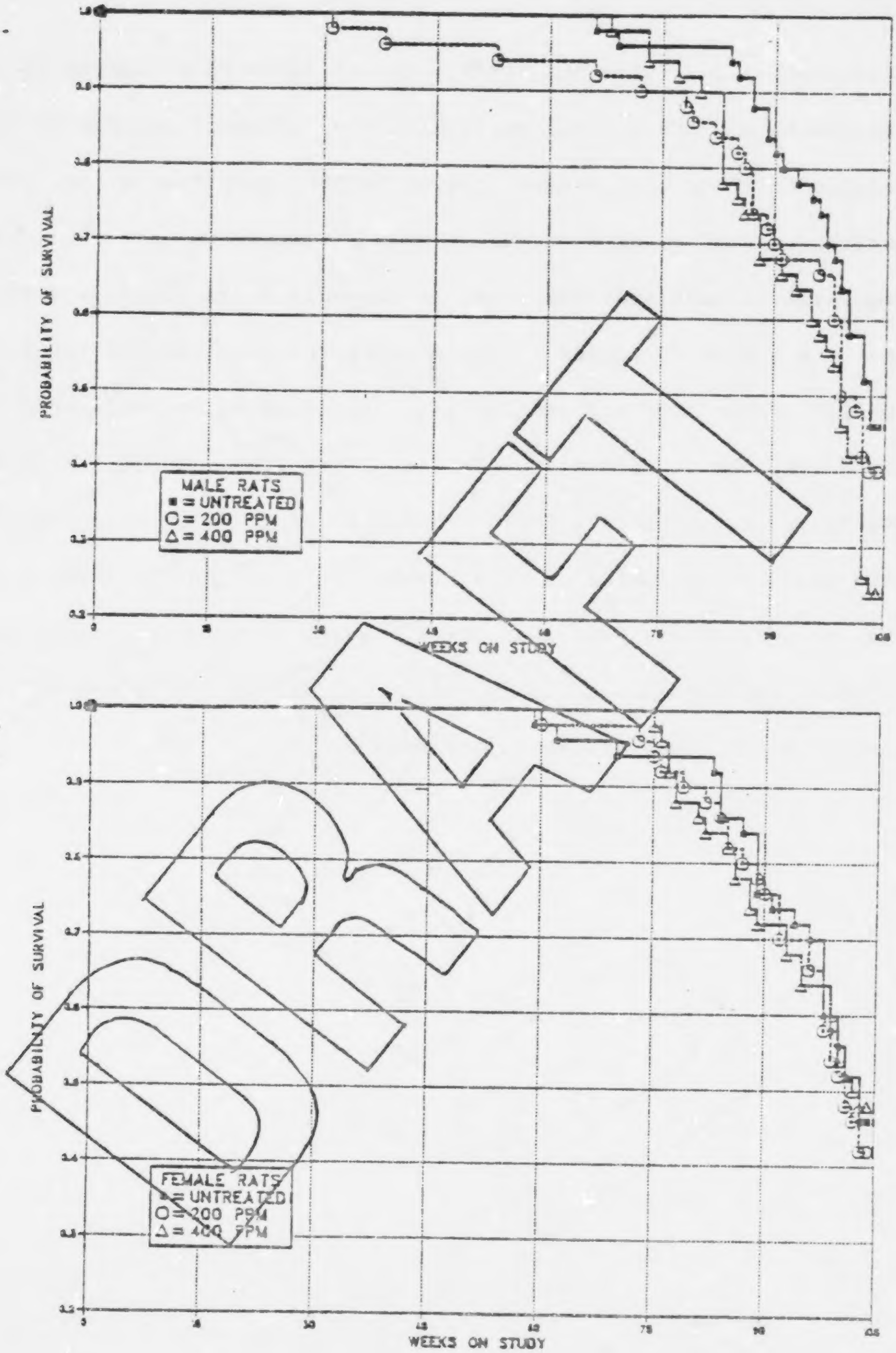

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FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO TETRACHLOROETHYLENE BY INHALATION FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the hematopoietic system, kidney, brain, testis, preputial gland, nasal cavity, adrenal gland, and forestomach. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

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Hematopoietic System: Mononuclear cell leukemia occurred with positive trends in males and females, and the incidences in the dosed groups were greater than those in the controls (Table 12). This hematopoietic neoplasm was recognized in its earliest stage as a diffuse infiltration of atypical mononuclear cells in the sinusoids of the liver and the interfollicular pulp of the spleen. In more advanced cases, there were infiltrations into virtually all organs and tissues.

The diagnoses of mononuclear cell leukemia were classified according to the extent of the disease as stage 1 (early), stage 2 (intermediate), or stage 3 (advanced). The following criteria were used:

> Stage 1--Spleen not enlarged or only moderately enlarged with few suspicious cells surrounding malipighian corpuscles of the spleen and only very few neoplastic cells in the blood vessels of the lung.
>
> Stage 2-- More severe than in the first category: spleen and/or liver only moderately enlarged with neoplastic cells in the liver sinusoids and the blood vessels of other organs.
>
> Stage 3--Enlarged spleen and liver with many neoplastic cells in the liver sinusoids and the blood vessels of other organs.

The distribution of stages of mononuclear cell leukemia in male and female rats is summarized in Table 13.

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TABLE 12. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE (a)

	Control	200 ppm	400 ppm
MALE			
Mononuclear Cell Leukemia (b)			
Overall Rates	28/50 (56%)	37/50 (74%)	37/50 (74%)
Adjusted Rates	64.6%	80.1%	90.8%
Terminal Rates	9/23 (39%)	11/20 (55%)	9/12 (75%)
Week of First Observation	66	53	68
Life Table Tests	P=0.004	P=0.046	P=0.004
Incidental Tumor Tests	P=0.097	P=0.023	P=0.104
FEMALE			
Mononuclear Cell Leukemia (c)			
Overall Rates	18/50 (36%)	30/50 (60%)	29/50 (58%)
Adjusted Rates	53.8%	71.4%	66.3%
Terminal Rates	9/23 (39%)	10/21 (48%)	10/24 (42%)
Week of First Observation	84	60	76
Life Table Tests	P=0.053	P=0.023	P=0.053
Incidental Tumor Tests	P=0.012	P=0.013	P=0.014

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at testing laboratory: 36/100, 36%; historical incidence in NTP studies: 458/1,727, 27% ± 9%
(c) Historical incidence at testing laboratory: 27/99, 27%; historical incidence in NTP studies: 307/1,772, 17% ± 6%

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TABLE 13. CLASSIFICATION OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

Group	Number of Rats with Mononuclear Cell Leukemia	Stage 1	Stage 2	Stage 3
MALE				
Control	28	5	3	20
200 ppm	37	6	7	24
400 ppm	37	4	6	27
FEMALE				
Control	18	3	5	10
200 ppm	30	6	6	18
400 ppm	29	2	6	21

Kidney: Both nonproliferative (karyomegaly and cytomegaly) and proliferative (tubular-cell hyperplasia, adenomas, and adenocarcinomas) changes were found in the kidney (Table 14).

Karyomegaly (reported as nuclear enlargement in CBDS, Appendix C) and cytomegaly were present primarily in the proximal convoluted tubules of the inner half of the cortex but were not necessarily limited to this area. Affected tubules showed two distinct patterns of changes. In one pattern, the cells were greatly enlarged and bulged into the lumens of the tubules. Cytoplasm was abundant, brightly eosinophilic, and granular. Basal striations and brush borders were frequently prominent. Nuclei were enlarged up to 10 times, rounded or oval, and contained deeply basophilic stippled or reticulated chromatin and a single nucleolus. Mitoses were occasionally present. In the second pattern, the lining cells of the tubules were flattened and spindle-shaped, and were thinner at the ends than at the center, where the greatly enlarged, basophilic, elongated nucleus bulged into the lumen.

Tubular cell hyperplasias were small circumscribed lesions often only a few hundred microns in diameter. Typically the cells were small with poorly defined basophilic cytoplasm and round open-faced nuclei. These lesions consisted of a nonseptated mass of cells which did not compress the surrounding parenchyma.

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TABLE 14. ANALYSIS OF RENAL LESIONS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
MALE			
Karyomegaly			
Overall Rates	1/49 (2%)	37/49 (76%)	47/50 (94%)
Tubular cell hyperplasia			
Overall Rates	0/49 (0%)	3/49 (6%)	5/50 (10%)
Tubular cell adenoma (a)			
Overall Rates	1/49 (2%)	3/49 (6%)	2/50 (4%)
Tubular cell adenocarcinoma			
Overall Rates	0/49 (0%)	0/49 (0%)	2/50 (4%)
Tubular cell adenoma or adenocarcinoma			
Overall Rates	1/49 (2%)	3/49 (6%)	4/50 (8%)
Adjusted Rates	4.3%	10.8%	22.4%
Terminal Rates	1/23 (4%)	1/20 (5%)	2/12 (17%)
Week of First Observation	104	91	83
Life Table Tests	P=0.054	P=0.259	P=0.070
Incidental Tumor Tests	P=0.197	P=0.286	P=0.114
FEMALE			
Karyomegaly			
Overall Rates	0/50 (0%)	8/49 (16%)	20/50 (40%)
Tubular cell hyperplasia			
Overall Rates	0/50 (0%)	0/49 (0%)	1/50 (2%)
Tubular cell adenoma			
Overall Rates	0/50 (0%)	0/49 (0%)	0/50 (0%)
Tubular cell adenocarcinoma			
Overall Rates	0/50 (0%)	0/49 (0%)	0/50 (0%)

(a) Historical incidence at testing laboratory: 0/100; historical incidence in NTP studies: 4/1,720, 0.2% ± 0.7%; no malignant tubular cell tumors have been observed.

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Tubular cell adenomas were well circumscribed and compressed the adjacent parenchyma. They were composed of varibly sized cuboidal, columnar, or polygonal cells that formed solid lobules separated by delicate connective tissue septa. Occasionally the cytoplasm was basophilic and granular or vacuolated and reticular. The nuclei were round and open faced, and mitoses were infrequent.

Tubular cell adenocarcinomas were usually larger than adenomas and may have invaded the adjacent parenchyma. The cells were more pleomorphic than in the adenomas and often contained large bizarre nuclei. Mitoses, while not common, were more frequent than in adenomas. Necrosis, hemorrhage, and cholesterol clefts were often present.

Tubular cell karyomegaly was observed at increased incidences in dosed male and female rats. Tubular cell hyperplasia was seen in dosed males and in one high dose female. Tubular cell adenomas or adenocarcinomas (combined) were observed at increased (although not statistically significant) incidences in dosed male but not dosed female rats (Table 14).

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Brain: Gliomas in male rats occurred with a significant positive trend by life table analysis (Table 15). The incidences in the dosed groups were not significantly greater than that in the controls by statistical comparisons, but four of these tumors were observed in the high dose males. Gliomas were also found in one control and two high dose females.

TABLE 15. ANALYSIS OF BRAIN TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
Glioma (a,b)			
Overall Rates	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	4.3%	0.0%	17.3%
Terminal Rates	1/23 (4%)	0/20 (0%)	0/12 (0%)
Week of First Observation	104		88
Life Table Tests	P=0.039	P=0.528N	P=0.083
Incidental Tumor Tests	P=0.103	P=0.528N	P=0.207

(a) Historical incidence of neuroglial cell tumors at testing laboratory: 2/97, 2%; historical incidence in NTP studies: 13/1,721, 0.8%

(b) Gliomas were found in 1/50 control, 0/50 low dose, and 2/50 high dose female rats.

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Testis: Interstitial cell tumors in male rats occurred with a significant positive trend, and the incidences in the dosed groups were significantly greater than that in the controls (Table 16).

TABLE 16. ANALYSIS OF TESTICULAR INTERSTITIAL CELL LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
Hyperplasia			
Overall Rates	5/50 (10%)	6/49 (17%)	4/50 (8%)
Tumor (a)			
Overall Rates	35/50 (70%)	39/49 (80%)	41/50 (82%)
Adjusted Rates	91.4%	97.5%	100.0%
Terminal Rates	20/23 (87%)	19/20 (95%)	12/12 (100%)
Week of First Observation	69	82	68
Life Table Tests	P<0.001	P=0.098	P=0.001
Incidental Tumor Tests	P=0.012	P=0.047	P=0.024
Hyperplasia or Tumor			
Overall Rates	40/50 (80%)	45/49 (92%)	45/50 (90%)

(a) Historical incidence at testing laboratory: 66/99, 67%; historical incidence in NTP studies: 1,511/1,703, 89% ± 8%

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Preputial Gland: Adenomas or carcinomas (combined) in male rats occurred with a positive trend by life table analysis (control, 3/50, 6%; low dose, 5/50, 10%; high dose, 6/50, 12%); the incidences in the dosed groups were not significantly greater than that in the controls.

Nasal Cavity: Thrombosis was observed at increased incidences in high dose male and dosed female rats (male: control, 9/50, 18%; low dose, 11/50, 22%; high dose, 19/50, 38%; female: control, 3/50, 6%; low dose, 10/50, 20%; high dose, 7/50, 14%). Squamous metaplasia was observed at increased incidences in dosed male rats (male: control, 0/50, low dose, 5/50, 10%; high dose, 5/50, 10%; female: control 2/50, 4%; low dose, 4/50, 8%; high dose, 2/50, 4%).

Adrenal Gland: The incidences of adrenal medulla hyperplasia in dosed males and adrenal cortical hyperplasia in high dose female rats were greater than those in the controls (medulla hyperplasia: male--control, 5/49, 10%; low dose, 14/49, 29%; high dose, 12/49, 24%; female--control, 7/50, 14%; low dose, 3/49, 6%; high dose, 4/47, 9%); cortical hyperplasia: male--control, 11/49, 22%; low dose, 5/49, 10%; high dose, 7/49, 14%; female--control, 4/50, 8%; low dose, 6/49, 12%; high dose, 11/47, 23%). Pheochromocytomas in male rats occurred with a significant positive trend by the life table test, and the incidence in the high dose group was significantly greater than that in the controls by the life table test (control, 22/49, 45%; low dose, 21/49, 43%; high dose, 23/49, 47%).

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Forestomach: Ulcers were observed at an increased incidence in high dose male rats (male: control, 0/48; low dose, 1/49, 2%; high dose, 5/49, 10%; female: control, 3/49, 6%; low dose, 4/49, 8%; high dose, 0/48).

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MICE

SINGLE-ADMINISTRATION STUDIES

All mice exposed at 2,971 or 3,786 ppm died before the end of the studies (Table 17). Mean body weight gain was not dose related. Hypoactivity and anesthesia in exposed animals were considered to be compound related.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-EXPOSURE INHALATION STUDIES OF TETRACHLOROETHYLENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
2,328	5/5	25.2 ± 0.9	27.0 ± 1.3	+1.8 ± 0.5
2,445	5/5	18.8 ± 0.7	24.4 ± 0.8	+5.6 ± 0.4
2,613	1/5	22.8 ± 1.1	21.0	+1.0
2,971	0/5	21.4 ± 0.5	(d)	(d)
3,786	0/5	19.2 ± 0.4	(d)	(d)
FEMALE				
2,328	3/5	21.0 ± 0.3	22.8 ± 0.3	+1.0 ± 0.6
2,445	5/5	16.6 ± 0.6	20.4 ± 0.4	+3.8 ± 0.4
2,613	3/5	19.4 ± 0.2	21.3 ± 0.3	+2.0 ± 0.0
2,971	0/5	19.2 ± 0.6	(d)	(d)
3,786	0/5	17.6 ± 0.5	(d)	(d)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) No data are presented due to the 100% mortality in this group.

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FOURTEEN-DAY STUDIES

None of the mice died before the end of the studies (Table 18). Dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia were observed in mice in the highest dose group. The final mean body weights of mice exposed at 1,750 ppm were 6% lower than that of controls for males and 7% lower for females. Cytoplasmic vacuolation (fat) of the hepatocytes was observed in 4/5 males at 875 ppm and in 5/5 males and 5/5 females at 1,750 ppm.

TABLE 18. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY INHALATION STUDIES OF TETRACHLOROETHYLENE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	25.4 ± 0.6	27.6 ± 1.0	+ 2.2 ± 0.7	--
100	5/5	25.2 ± 0.6	28.4 ± 0.7	+ 3.2 ± 0.2	102.9
200	5/5	25.4 ± 0.4	28.6 ± 0.2	+ 3.2 ± 0.5	103.6
425	5/5	24.8 ± 0.2	27.0 ± 0.7	+ 2.2 ± 0.6	97.8
875	5/5	25.0 ± 0.3	27.4 ± 0.7	+ 2.4 ± 0.4	99.3
1,750	5/5	24.4 ± 0.4	26.0 ± 0.8	+ 1.6 ± 0.4	94.2
FEMALE					
0	5/5	19.8 ± 0.5	24.8 ± 0.5	+ 5.0 ± 0	--
100	5/5	19.0 ± 0.6	23.6 ± 0.6	+ 4.6 ± 0.4	95.2
200	5/5	19.0 ± 0.5	24.2 ± 0.5	+ 5.2 ± 0.4	97.6
425	5/5	19.4 ± 0.4	23.2 ± 0.4	+ 3.8 ± 0.4	93.5
875	5/5	20.0 ± 0.3	24.6 ± 0.4	+ 4.6 ± 0.2	99.2
1,750	5/5	19.0 ± 0.3	23.0 ± 0.5	+ 4.0 ± 0.3	92.7

(a) Number surviving/number in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean

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THIRTEEN-WEEK STUDIES

Two of 10 males and 4/10 females that were exposed to tetrachloroethylene at 1,600 ppm died before the end of the studies (Table 19). On the second day of exposure only, all mice in the 1,600-ppm group were uncoordinated and unconscious, mice in the 800-ppm group were panting and appeared irritated, and mice in the 400-ppm group were hunched and did not move. The final mean body weight of males exposed at 1,600 ppm was 8% lower than that of the controls. Final mean body weights of dosed and control female mice were comparable. Liver lesions (leukocytic infiltration, centrolobular necrosis, and bile stasis) were seen in mice exposed at 400, 800, or 1,600 ppm (Table 20). Karyomegaly (nuclear enlargement) of the renal tubule epithelial cells was observed in 7/10 males and 7/10 females exposed at 1,600 ppm.

Dose Selection Rationale: Because of the incidence of deaths at 1,600 ppm and hepatic and renal lesions observed at lower doses, exposure concentrations selected for mice for the 2-year studies were 100 and 200 ppm tetrachloroethylene.

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TABLE 19. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF TETRACHLOROETHYLENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	27.4 ± 0.8	32.9 ± 0.8	+ 5.5 ± 0.3	--
100	10/10	27.4 ± 0.7	34.5 ± 0.8	+ 7.1 ± 0.9	104.9
200	10/10	26.3 ± 1.1	32.2 ± 0.8	+ 5.9 ± 1.6	97.9
400	10/10	25.4 ± 0.8	32.8 ± 0.6	+ 7.4 ± 0.6	99.7
800	10/10	27.0 ± 0.8	33.3 ± 0.6	+ 6.3 ± 0.7	101.2
1,600	(d) 8/10	27.4 ± 0.6	30.4 ± 1.5	+ 2.9 ± 1.3	92.4
FEMALE					
0	10/10	21.5 ± 0.5	27.5 ± 0.8	+ 6.0 ± 0.7	--
100	10/10	22.0 ± 0.6	28.6 ± 0.7	+ 6.6 ± 0.3	104.0
200	10/10	22.0 ± 0.4	28.2 ± 0.6	+ 6.2 ± 0.4	102.5
400	10/10	19.6 ± 0.6	29.5 ± 0.9	+ 9.9 ± 0.6	107.3
800	10/10	20.5 ± 0.6	28.2 ± 0.7	+ 7.7 ± 0.5	102.5
1,600	(e) 6/10	21.8 ± 0.4	27.5 ± 0.5	+ 5.5 ± 0.5	100.0

(a) Number surviving/number in group

(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.

(c) Mean body weight change of the survivors of the group ± standard error of the mean

(d) Week of death: 12, 14

(e) Week of death: 1, 8, 12, 13

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TABLE 20. INCIDENCE AND SEVERITY OF LIVER AND KIDNEY LESIONS IN MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF TETRACHLOROETHYLENE

Group	Liver: Leukocytic Infiltration/Centrolobular Necrosis/Bile Stasis Male	Female	Liver Mitotic Alteration Male	Female	Kidney Karyomegaly Male	Female
Control	(a) 0/10	0/10	0/10	0/10	0/10	0/10
100 ppm	--	--	--	--	0/10	0/10
200 ppm	0/10	0/10	3/10 (1.0)	0/10	6/10 (1.0)	8/10 (1.0)
400 ppm	8/10 (1.4)	5/10 (1.2)	5/10 (1.6)	0/10	10/10 (1.6)	10/10 (2.0)
800 ppm	10/10 (1.8)	10/10 (1.2)	5/10 (2.2)	0/10	10/10 (1.4)	10/10 (1.5)
1,600 ppm	10/10 (2.2)	8/9 (1.6)	1/10 (1.0)	0/9	7/7 (1.6)	6/7 (1.7)

(a) Incidence of lesion; mean severity score of affected animals is in parentheses: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control male and dosed and control female mice were comparable throughout the studies (Table 21 and Figure 3).

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TABLE 21. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

Weeks on Study	Control		100 ppm			200 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	23.3	50	23.0	99	50	21.8	94	50
1	25.4	50	24.9	98	50	23.6	93	50
2	25.3	50	26.6	105	50	27.7	109	50
3	25.9	50	27.3	105	50	27.9	108	50
4	27.6	50	28.9	105	50	29.8	108	50
5	31.2	50	28.8	92	50	28.5	91	50
6	28.9	50	27.7	96	50	29.3	101	50
7	29.4	50	29.2	99	50	30.7	104	50
8	28.9	50	31.1	108	50	30.6	106	50
9	30.2	50	31.5	104	50	27.2	90	50
10	30.3	50	31.0	102	50	28.1	93	50
11	30.1	50	31.8	106	50	32.1	107	50
12	30.2	50	32.6	108	50	31.9	106	50
13	31.2	50	31.1	100	50	31.6	101	50
17	31.8	50	32.1	101	50	33.2	104	50
21	33.3	50	33.3	100	50	34.0	102	50
25	34.2	50	33.5	98	50	35.5	104	50
29	34.0	50	33.0	97	50	35.0	103	50
34	36.7	50	33.8	92	50	37.7	103	50
38	35.5	50	35.5	100	50	35.5	100	50
43	38.1	50	36.3	95	50	37.7	99	50
47	37.4	50	36.9	99	49	40.1	107	50
51	36.7	50	36.9	101	49	38.4	105	50
55	37.4	50	36.3	97	49	39.0	104	50
60	37.5	50	36.8	98	48	38.9	104	50
64	37.1	50	38.9	105	46	39.4	106	48
69	37.9	50	36.9	97	45	38.6	102	48
73	38.5	50	37.5	97	45	39.0	101	48
78	38.3	50	37.2	97	43	38.5	101	45
82	38.4	50	36.8	96	42	39.3	102	42
86	38.2	50	37.7	99	[illegible]	38.5	101	40
90	38.1	49	37.1	97	35	38.5	101	39
95	37.0	49	36.2	98	33	38.7	105	37
99	36.6	46	37.1	101	27	37.6	103	35
FEMALE								
0	18.0	49	18.0	100	50	18.2	101	50
1	20.0	49	18.9	95	50	19.8	99	49
2	20.0	49	20.9	105	50	20.4	102	49
3	21.1	49	21.2	100	50	22.5	107	49
4	22.0	48	22.7	103	50	23.0	105	49
5	23.5	47	23.3	99	50	23.0	98	49
6	22.0	47	22.3	101	48	24.0	109	49
7	23.0	47	22.8	99	48	24.2	105	49
8	23.5	47	24.0	102	46	24.3	103	49
9	24.1	47	25.8	107	46	19.8	82	49
10	24.1	47	25.6	106	46	25.9	107	49
11	24.6	47	26.2	107	46	26.1	106	49
12	25.6	47	25.9	101	46	26.2	102	49
13	24.9	47	24.6	99	45	27.9	112	49
17	26.2	46	26.9	103	44	27.5	105	49
21	27.1	46	27.5	101	44	27.7	102	49
25	27.8	46	28.0	101	43	28.4	102	49
28	28.9	46	28.4	98	43	28.9	100	49
34	30.0	46	28.9	96	43	30.0	100	49
38	30.0	46	29.5	98	42	28.6	95	48
43	32.0	46	30.0	94	42	30.8	96	48
47	32.0	46	30.0	94	42	31.4	98	48
51	32.0	46	30.8	96	42	31.5	98	48
55	32.0	46	30.3	95	42	32.0	100	47
60	31.9	45	31.7	99	42	31.9	100	47
64	32.0	45	31.7	99	42	33.7	105	47
69	33.6	45	32.5	97	42	33.1	99	46
73	33.2	44	31.8	96	42	33.5	101	44
78	33.8	44	32.0	95	40	33.7	100	43
82	34.3	44	31.5	92	40	33.6	98	42
86	33.4	43	32.2	96	39	33.1	99	40
90	32.9	43	32.4	98	38	30.6	93	36
95	32.7	42	32.3	99	35	31.8	97	33
99	32.4	39	32.3	100	35	32.1	99	27

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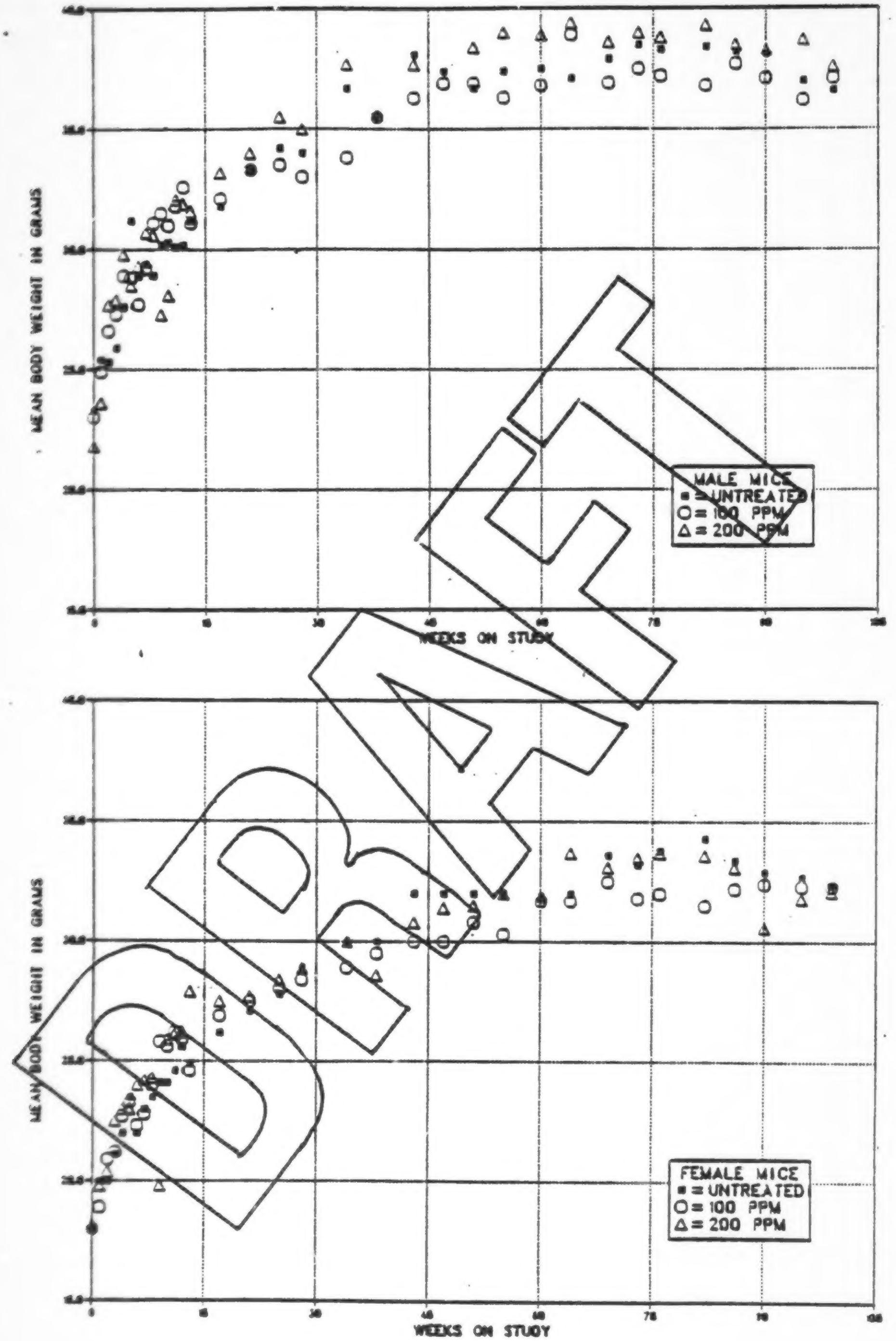

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FIGURE 3. GROWTH CURVES FOR MICE EXPOSED TO TETRACHLOROETHYLENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice exposed to tetrachloroethylene at the concentrations used in these studies and those of the controls are shown in the Kaplan and Meier curves in Figure 4. The survival of the low dose (after week 74) and high dose (after week 78) male groups and the high dose female group (after week 90) was significantly lower than that of the controls (Table 22).

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TABLE 22. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

	Control	100 ppm	200 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	3	25	18
Animals missexed	1	0	0
Killed at termination	46	25	32
Survival P values (c)	0.002	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	17	30
Accidentally killed	2	2	1
Animals missexed	1	0	0
Killed at termination	36	31	17
Died during termination period	0	0	2
Survival P values (c)	<0.001	0.241	<0.001

(a) Terminal kill period: week 104

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

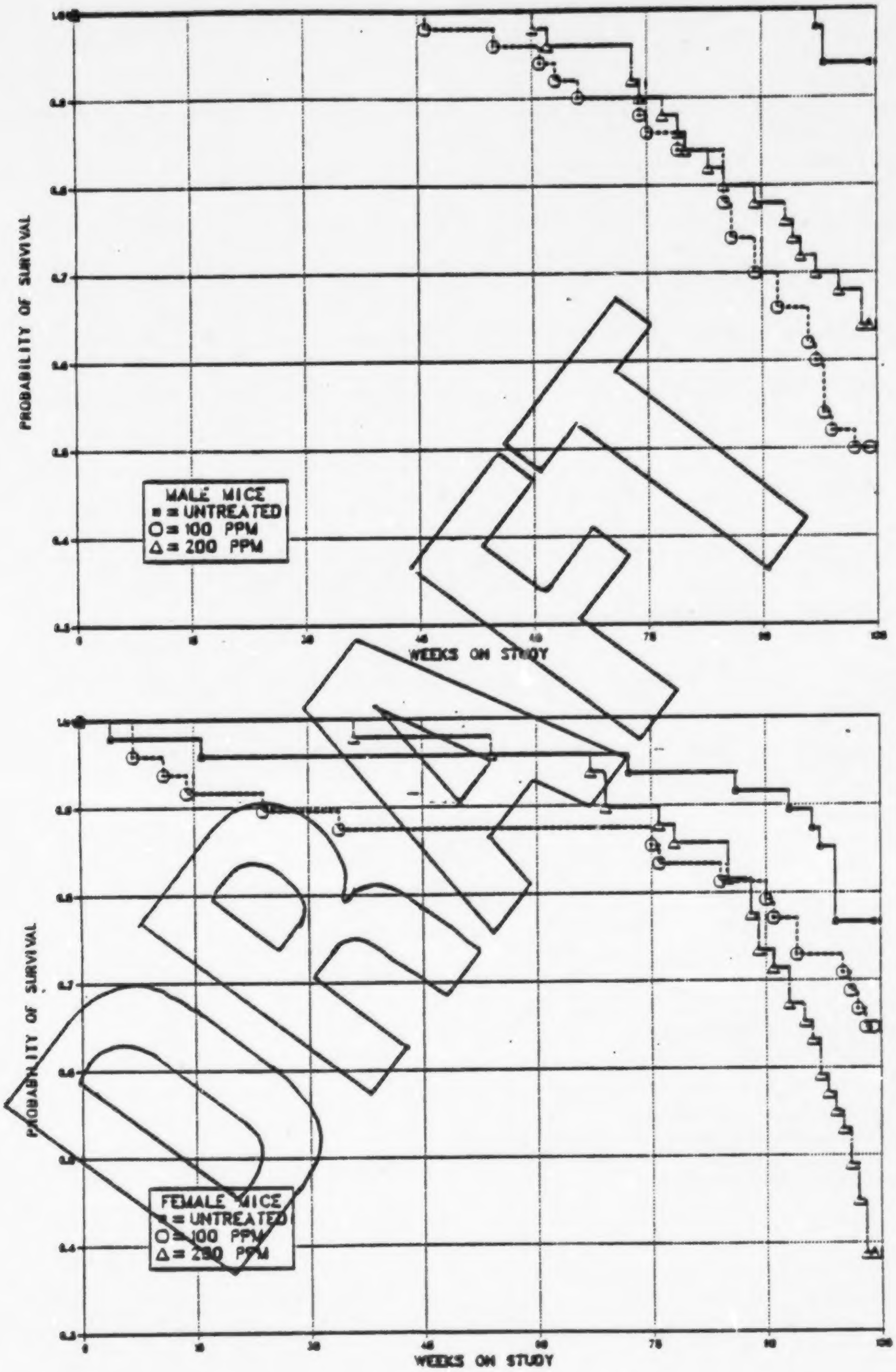

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FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO TETRACHLOROETHYLENE BY INHALATION FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, kidney, and lung. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

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Liver: Degeneration was observed at increased incidences in dosed male mice (control, 2/49, 4%; low dose, 8/49, 16%; high dose, 14/50, 28%) and high dose female mice (control, 1/49, 2%; low dose, 2/50, 4%; high dose, 13/50, 26%); necrosis was observed at increased incidences in dosed male (control, 1/49, 2%; low dose, 6/49, 12%; high dose, 15/50, 30%) and high dose female mice (control, 3/48, 6%; low dose, 5/50, 10%; high dose, 9/50, 18%); nuclear inclusions were observed at increased incidences in dosed male mice (control, 2/49, 4%; low dose, 5/49, 10%; high dose, 9/50, 18%). Hepatic degeneration was characterized by a variety of histologic features, including cytoplasmic vacuolation, hepatocellular necrosis, inflammatory cell infiltrates, pigment in cells, oval cell hyperplasia, and regenerative foci. Hepatocellular adenomas in males, hepatocellular carcinomas in males and females, and hepatocellular adenomas or carcinomas (combined) in males and females occurred with significant positive trends (Table 23). The incidences of hepatocellular adenomas in high dose males and hepatocellular carcinomas and hepatocellular adenomas or carcinomas (combined) in dosed mice were significantly greater than those in the controls.

Hepatocellular carcinomas metastasized to the lung in two control males and seven low dose and one high dose males and in two low dose and seven high dose females. Additional hepatocellular carcinomas metastasized to the pulmonary artery in one low dose male, to the pulmonary vein in one low dose and one high dose male, and to multiple organs in one low dose male mouse (Appendix B, Tables B3 and B4).

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TABLE 23. ANALYSIS OF LIVER TUMORS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE (a)

	Control	100 ppm	200 ppm
MALE			
Hepatocellular Adenoma			
Overall Rates	11/49 (22%)	8/49 (16%)	18/50 (36%)
Adjusted Rates	23.9%	29.9%	52.4%
Terminal Rates	11/46 (24%)	7/25 (28%)	16/32 (50%)
Week of First Observation	104	89	73
Life Table Tests	P=0.005	P=0.345	P=0.006
Incidental Tumor Tests	P=0.009	P=0.463	P=0.013
Hepatocellular Carcinoma			
Overall Rates	7/49 (14%)	25/49 (51%)	26/50 (52%)
Adjusted Rates	14.9%	58.3%	58.3%
Terminal Rates	6/46 (13%)	8/25 (32%)	14/32 (44%)
Week of First Observation	98	63	60
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P=0.002	P=0.016	P=0.001
Hepatocellular Adenoma or Carcinoma (b)			
Overall Rates	16/49 (33%)	31/49 (63%)	40/50 (80%)
Adjusted Rates	34.0%	73.0%	86.8%
Terminal Rates	15/46 (33%)	14/25 (56%)	26/32 (81%)
Week of First Observation	98	63	60
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.017	P<0.001
FEMALE			
Hepatocellular Adenoma			
Overall Rates	3/48 (6%)	6/50 (12%)	2/50 (4%)
Adjusted Rates	7.5%	18.7%	6.1%
Terminal Rates	1/36 (3%)	5/31 (16%)	0/19 (0%)
Week of First Observation	96	102	78
Life Table Tests	P=0.479	P=0.182	P=0.641N
Incidental Tumor Tests	P=0.325N	P=0.193	P=0.213N
Hepatocellular Carcinoma			
Overall Rates	1/48 (2%)	13/50 (26%)	36/50 (72%)
Adjusted Rates	2.8%	35.5%	91.7%
Terminal Rates	1/36 (3%)	8/31 (26%)	16/19 (84%)
Week of First Observation	104	76	67
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma or Carcinoma (c)			
Overall Rates	4/48 (8%)	17/50 (34%)	38/50 (76%)
Adjusted Rates	10.1%	46.7%	92.2%
Terminal Rates	2/36 (6%)	12/31 (39%)	16/19 (84%)
Week of First Observation	96	76	67
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at testing laboratory: 28/100, 28%; historical incidence in NTP studies: 540/1,784, 30% ± 8%
(c) Historical incidence at testing laboratory: 5/100, 5%; historical incidence in NTP studies: 147/1,781, 8% ± 5%

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Kidney: Nephrosis was observed at increased incidences in dosed female mice; casts were observed at increased incidences in dosed male and high dose female mice; and karyomegaly of the tubular cells was observed at increased incidences in dosed mice (Table 24). The severity of the renal lesions was dose related. One low dose male had a renal tubular cell adenocarcinoma.

Lung: Acute passive congestion was observed at increased incidences in dosed mice (male: control, 1/49; low dose, 8/49; high dose, 10/50; female: control, 1/48; low dose, 5/50; high dose, 6/50).

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TABLE 24: NUMBERS OF MICE WITH NONNEOPLASTIC LESIONS OF THE KIDNEY IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

Lesion	Control	100 ppm	200 ppm
MALE			
Number of animals examined	49	49	50
Cast	3	9	15
Tubular cell karyomegaly	4	17	46
Nephrosis	22	24	28
FEMALE			
Number of animals examined	48	49	50
Cast	4	4	15
Tubular cell karyomegaly	0	16	38
Nephrosis	5	14	25

IV. DISCUSSION AND CONCLUSIONS

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Toxicology and carcinogenicity studies were conducted by administering tetrachloroethylene (99.9% pure) by inhalation to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice for 6 hours per day, 5 days per week, for 103 weeks. The exposure concentrations used in these studies (0 [chamber controls], 200, or 400 ppm in rats and 0, 100, or 200 ppm in mice) were selected on the basis of results of 13-week inhalation studies in which groups of rats and mice of each sex were exposed to tetrachloroethylene at concentrations ranging from 100 to 1,600 ppm for 6 hours per day, 5 days per week.

Thirteen-Week Studies

During the 13-week studies in rats, exposure to tetrachloroethylene at 1,600 ppm killed 4/10 males and 7/10 females. The final mean body weights of animals that survived exposure at the highest concentration were reduced relative to those of the controls (male, 20%; female, 11%). Histopathologic changes observed included pulmonary congestion in animals exposed at 1,600 ppm (male, 8/10; female, 7/10) but not at 800 ppm. A dose-related increase in the incidence of hepatic congestion was observed in both sexes, but the severity of this effect in animals exposed at 200-800 ppm was considered to be minimal to mild. Affected animals in the 1,600-ppm groups (male, 7/10; female, 8/9) exhibited mild to severe hepatic congestion.

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In mice, exposure at 1,600 ppm for 13 weeks killed 2/10 males and 4/10 females. As in rats, the final mean body weights of male mice that survived exposure at 1,600 ppm were somewhat lower than those of the controls. Minimal to mild microscopic liver and kidney changes were observed in mice exposed at 200-1,600 ppm tetrachloroethylene. The liver changes included leukocytic infiltration, centrolobular necrosis, bile stasis, and mitotic alteration. The kidney changes were described as karyomegaly of the tubular epithelial cells and were considered to be of minimal severity in the affected 6/10 males and 8/10 females exposed at 200 ppm.

This kidney lesion has been observed in earlier gavage studies of tetrachloroethylene (NTP, unpublished results), pentachloroethane (NTP, 1983), and trichloroethylene (NTP, unpublished results). These changes are the earliest renal effects produced by these chemicals and are usually followed by cytomegaly, renal tubular epithelial cell hyperplasia, and tubular dilatation. Although kidney lesions were not found in the rats exposed to tetrachloroethylene for 13 weeks in these studies, both rats and mice in the aforementioned studies were affected.

Selection of exposure concentrations for the 2-year studies in rats and mice was made on the basis of the lethality at 1,600 ppm in both species and the production of liver and kidney lesions at the lower concentrations. Although the changes produced at the lower concentrations were generally minimal to mild, earlier experiences with chlorinated ethanes and ethylenes indicated that these changes may be progressive. This is particularly true of the kidney lesions. In earlier 2-year gavage studies on trichloroethylene and tetrachloroethylene, the survival of rats and mice was adequate for approximately 40 weeks, and then high incidences of early deaths among

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dosed animals occurred for the remainder of the studies. The early deaths in dosed rats in the earlier studies were always sufficient to compromise the sensitivity of the assays.

Two-Year Studies

Survival of Rats: Exposure at 400 ppm tetrachloroethylene reduced the survival of male rats (control, 23/50; low dose, 20/50; high dose, 12/50) but not that of the females (control, 23/50; low dose, 21/50; high dose, 24/50). Most of the unscheduled deaths in the high dose male group, 33/38, 87%, occurred late in the study (week 82 or later) and may have been related to a high incidence of mononuclear cell leukemia. There were positive trends in the incidences of leukemia in male and female rats, and the incidence in the high dose male group was greater than that in the control group (control, 28/50; low dose, 37/50; high dose, 37/50; P=0.004).

Mononuclear cell leukemia develops spontaneously in F344 and Wistar Furth rats (Moloney et al., 1969, 1970; Davey and Moloney, 1970) and has been estimated to be fatal within 2-8 weeks of onset (Stromberg and Vogtsberger, 1983). To determine if the increased incidence of leukemia in the dosed males may have contributed to the excess in unscheduled deaths among high dose males, the progression of the disease in all affected animals was determined microscopically. The diagnoses of mononuclear cell leukemia were classified as stage 1 (early stage of the disease), stage 2 (intermediate stage), or stage 3 (advanced and probably fatal). The diagnostic criteria are detailed in the results section.

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The results summarized in Table 25 show the comparative incidences of stage-3 mononuclear cell leukemia in rats that died before the scheduled termination of the studies and in rats that lived to the end of the study. The percent of animals in each dose group with stage-3 mononuclear cell leukemia was consistently higher among animals that died early than among animals that lived to the end of the study. When overall unexplained deaths are considered, 11 more high dose males than controls (41% more) died before the scheduled termination of the study. If advanced stage leukemias are discounted, there are only three (25%) more unexplained deaths in the high dose male group. These facts suggest a relationship between the incidence of mononuclear cell leukemia and the excess early deaths in the high dose male group.

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TABLE 25. COMPARATIVE INCIDENCES OF STAGE-THREE MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

Group	Early Death (a)	Scheduled Death (b)
MALE		
Control	(c) 15/27 (55%)	5/23 (22%)
200 ppm	21/30 (70%)	3/20 (15%)
400 ppm	23/38 (60%)	4/12 (33%)
FEMALE		
Control	7/27 (26%)	3/23 (13%)
200 ppm	15/29 (52%)	3/21 (14%)
400 ppm	19/26 (73%)	2/24 (8%)

(a) Includes only those animals that died before week 104
(b) Includes only those animals that lived for 104 weeks
(c) Number of animals with stage-3 mononuclear cell leukemia/number examined

Survival of Mice: Exposure to tetrachloroethylene at 100 or 200 ppm reduced survival of male mice and at 200 ppm reduced survival of female mice. As in the rat studies, most of the early deaths in dosed mice occurred after week 82. Among males, the survival rate at week 82 was 50/50 in controls, 42/50 in the low dose group, and 42/50 in the high dose group; among females, it was 44/50 in the controls, 40/50 in the low dose group, and 42/50 in the high dose group. It should be noted that the survival of the chamber control male mice was unusually high; 46/50 lived to the termination of the study. The unscheduled deaths in dosed mice may have been influenced by the high incidence of hepatocellular carcinomas. There were dose-related increases in the incidences of this tumor among early death mice (male: control, 1/3, 33%; low dose, 17/24, 71%; high dose, 12/18, 67%; female: control, 0/12; low dose, 5/19, 26%; high dose, 20/31, 65%). Because of the small number of early deaths in the male mouse controls, hepatocellular neoplasms observed in dosed male mice dying before the end of the study were given relatively little weight by the incidental tumor test. Nevertheless, the increased incidences of hepatocellular neoplasms in dosed male and female mice were clear cut, regardless of which statistical test was used in the data analysis (Table 23).

Body Weight Gains in Rats and Mice: Body weight gains by dosed rats and mice were not consistently affected by exposure to tetrachloroethylene. Mean body weights for dosed rats were never more than 8% lower than those of the chamber controls. During week 9 of the studies in mice, the mean body weight of high dose females was only 82% that of the chamber controls. However, the validity of this observation is

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questionable, since during week 8 the high dose females weighed 103% of controls and during week 10 they weighed 107% of controls.

Mononuclear Cell Leukemia in Rats: There were positive trends for the incidences of mononuclear cell leukemia in male and female rats exposed to tetrachloroethylene (male: control, 28/50; low dose, 37/50; high dose, 37/50; female: control, 18/50; low dose, 30/50; high dose, 29/50). The incidences of mononuclear cell leukemia in male and female control rats of these studies were greater than the mean historical untreated control incidences for either this laboratory (male: 36/100, 36%; female: 27/99, 27%) or the Program (male: 458/1,727, 27%; female: 307/1,772, 17%). The concurrent control rates for these studies were similar to those of the dichloromethane studies conducted in this laboratory at the same time (NTP, 1985).

There is convincing evidence that these leukemias were related to many of the early deaths among both male and female rats dosed with tetrachloroethylene. Most leukemias were diagnosed as being in an advanced and probably fatal stage (Table 13), and the incidences of these advanced neoplasms in animals that died early (between week 82 and 103) consistently exceeded the incidences observed in animals of the same dose groups that survived to the scheduled termination of the studies. Therefore life table analyses are the appropriate statistical procedures for these lesions, and these tests indicate significant increases in incidences of leukemias in male rats dosed with either 200 ppm (P=0.046) or 400 ppm (P=0.004). In females, life table analysis of

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overall leukemia rates revealed a significant increase in the 200-ppm group (P=0.023) and a marginal effect (P=0.053) in the 400-ppm group.

The results summarized in Table 25 show that, although there were no tetrachloroethylene-related differences in the numbers of females that died before the scheduled termination of the study, there was a dose-related increase in the percent of females that died early and had stage-3 mononuclear cell leukemia (control, 26%; low dose, 52%; high dose, 73%). Because of this observation, a special statistical analysis was conducted. In this analysis, only the incidences of stage-3 mononuclear cell leukemias in rats were considered. The results of this analysis are shown in Table 26. This analysis revealed positive trends and significant increases in the incidences of stage-3 mononuclear cell leukemia in male and female rats exposed at 400 ppm tetrachloroethylene.

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TABLE 26. LIFE TABLE ANALYSIS OF THE INCIDENCES OF STAGE-THREE MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
MALE			
Overall Rates	20/50 (40%)	24/50 (48%)	27/50 (54%)
Adjusted Rates	48.9%	54.8%	69.7%
Terminal Rates	5/23 (22%)	3/20 (15%)	4/12 (33%)
P value (trend)	0.024		
P value (pairwise comparisons)		0.181	0.022
FEMALE			
Overall Rates	10/50 (20%)	18/50 (36%)	21/50 (42%)
Adjusted Rates	30.7%	46.1%	47.1%
Terminal Rates	3/23 (13%)	3/21 (14%)	2/24 (8%)
P value (trend)	0.027		
P value (pairwise comparisons)		0.065	0.029

Examination of the time to diagnosis of stage-3 mononuclear cell leukemia in female rats is also suggestive of a significant effect of tetrachloroethylene. The results in Table 27 show that between weeks 80 and 103 there were no remarkable differences in the numbers of deaths among the female rats in the three groups (see denominators of effect ratios). There was, however, a dose-related increase in the numbers of animals that died with stage-3 mononuclear cell leukemia. The initial stage-3 mononuclear cell leukemia in control rats was diagnosed in an animal that died during week 96 (when the 15th death among control females occurred). At week 96, there were eight advanced leukemias among 18 early death animals in the 400-ppm group. The first diagnoses of advanced leukemias in dosed animals were made during weeks 60 (200-ppm group) and 76 (400-ppm group). These results indicate that mononuclear cell leukemia, a spontaneously occurring neoplasm in F344/N rats, developed earlier in females that were exposed at 200 or 400 ppm tetrachloroethylene by inhalation. This observation is confirmed by the Kaplan-Meier curve for stage-3 mononuclear cell leukemia in female rats (Figure 5). The Kaplan-Meier curve for stage-3 mononuclear cell leukemia in male rats shows a less pronounced effect.

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TABLE 27. CUMULATIVE INCIDENCES OF MONONUCLEAR CELL LEUKEMIA IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Week on Study				
	80	85	90	96	103
Control	(a) 0/3	0/7	0/12	1/15	7/27
200 ppm	3/5	6/9	7/12	8/17	15/29
400 ppm	3/6	5/9	9/14	13/18	19/26

(a) Number of animals with stage-3 mononuclear cell leukemia/number of animals that died up to the week indicated

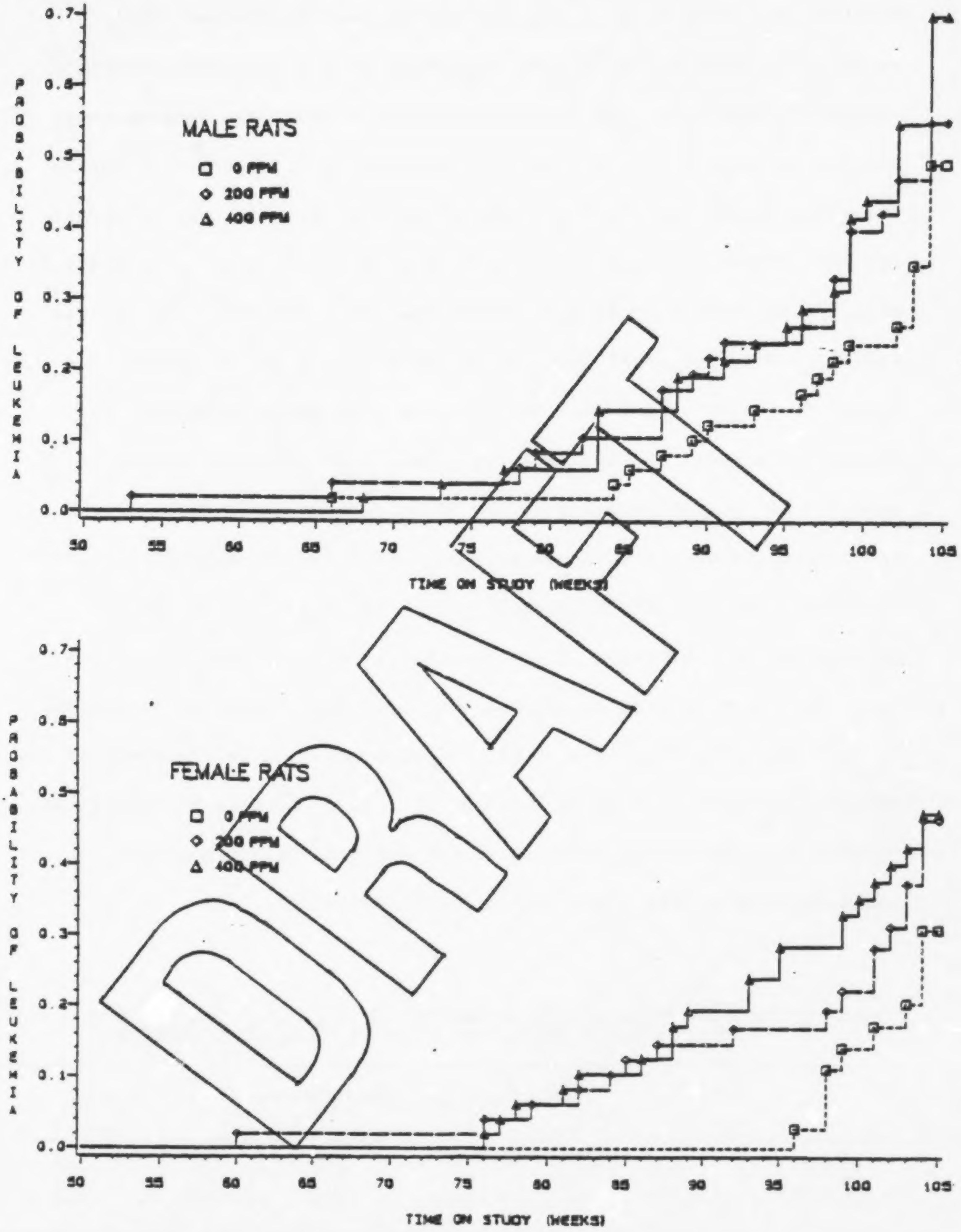

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FIGURE 5. KAPLAN-MEIER CURVES FOR STAGE-THREE LEUKEMIA INCIDENCE IN RATS EXPOSED TO TETRACHLOROETHYLENE BY INHALATION FOR TWO YEARS

__Kidney Effects in Rats__: The nephropathy normally observed in aging F344/N rats was observed in the animals of these studies. In addition, both sexes exhibited renal tubular cell karyomegaly (male: control, 1/49; low dose, 37/49; high dose, 47/50; female: control, 0/50; low dose, 8/49; high dose, 20/50). In males, this effect was accompanied by renal tubular cell hyperplasia (control, 0/49; high dose, 3/49; low dose, 5/50). A single high dose female also had renal tubular cell hyperplasia. These effects have been observed in earlier gavage studies on tetrachloroethylene and trichloroethylene; data from these studies are being reviewed. NTP's earlier analyses of these lesions indicate that they are early stages of a group of kidney changes that develop in rats after prolonged exposure to chlorinated ethanes and ethylenes. The earliest change is renal tubular cell karyomegaly, which is followed by the development of bizarre nuclear shapes, and cytomegaly with the cells assuming the shape of the nucleus. A more advanced stage of the syndrome is tubular cell hyperplasia, in which the proliferating cells fill the renal tubules. The effect is not unique to F344/N rats, as it has been observed in male and female rats of the Osborne-Mendel, August, Sprague-Dawley, ACI, and Marshall strains exposed to chlorinated ethylenes.

In the present studies, in addition to the renal tubular cell karyomegaly and hyperplasia, renal tubular cell adenomas and adenocarcinomas were detected in male rats. The combined incidences of the neoplasms were 1/49 for controls, 3/49 for the low dose group, and 4/49 for the high dose group. No renal tubular cell tumors were detected in female rats. The incidences of these neoplasms in male rats

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were not statistically significant (P>0.05). However, the induction of these lesions in rats, like the nonproliferative lesions described above, are characteristic effects of the long-term administration of chlorinated ethanes and ethylenes. NTP has noted them in gavage studies of pentachloroethane, trichloroethylene (in five strains of rats), and tetrachlororethylene (in five strains of rats). Since these lesions appeared consistently in dosed animals but not in controls in these long-term studies, they are considered to be caused by exposure to tetrachloroethylene in the present studies. Both the nonproliferative and proliferative changes produced by tetrachloroethylene are similar to the renal lesions described in rats exposed to petroleum products (Mehlman et al., 1984).

Respiratory Tract Effects in Rats: The nasal cavities of both sexes of rats were observed to have dose-related increases in the incidences of thromboses and squamous metaplasia. There were, however, no neoplastic changes. Similarly, there were no increases in pulmonary neoplasms in rats.

Other Findings in Rats: Four high dose male, two high dose female, one control male, and one control female rat exhibited gliomas of the brain. The incidence of this tumor in the male high dose group is above the control incidence at this laboratory (1/97, 1%) or in the overall Program (13/1,721, 0.8%). Unlike the kidney lesions described above, however, compound-related brain tumors have never been observed in earlier NTP studies of tetrachloroethylene, trichloroethylene, or pentachloroethane. The incidences of these tumors in the high dose

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groups in these studies are not statistically significant, and gliomas were observed in the control groups; for these reasons, the gliomas are considered to be a chance finding rather than a tetrachloroethylene-induced neoplasm.

The incidence of testicular interstitial cell tumors in male rats was increased relative to the control incidence. This tumor is common in aging male F344/N rats, and the incidences in both dosed groups are similar to the overall incidence in the Program (1,511/1,703, 89%). Also, when interstitial cell hyperplasia is combined with interstitial cell tumors, the magnitude of the apparent effect is somewhat diminished (control, 40/50; low dose, 45/49; high dose, 45/50). Therefore, although the incidences in dosed rats exceed both concurrent controls and the historical control rate for this laboratory (66/99, 67%), the marginal increase is not considered to be related to tetrachloroethylene exposure.

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Adenomas or carcinomas (combined) of the preputial gland were increased in a dose-related manner in male rats. However, since these tumors are not considered to be life threatening the incidental tumor test is the appropriate method for statistical analysis, and this test did not show statistical significance. Also, the incidences of neither adenomas nor carcinomas per se were significantly increased by tetrachloroethylene exposure.

Liver Effects in Mice: Dose-related increases in liver degeneration, hepatocellular necrosis, and hepatocellular nuclear inclusion were noted in both male and female mice exposed to tetrachloroethylene. In addition, tetrachloroethylene at both concentrations increased the incidences of hepatocellular neoplasms in males and females (adenomas or carcinomas combined: male--control, 16/49; low dose, 31/49; high dose, 40/50; female--control, 4/48; low dose, 17/50; high dose, 38/50). In male mice, hepatocellular carcinomas metastasized to the lungs in 2/49 of the controls, 7/49 of the low dose group, and 1/50 of the high dose group. One hepatocellular carcinoma metastasized to the pulmonary artery in a low dose male mouse. Hepatocellular carcinomas were also found in the lungs of 0/48 of the female controls, 2/50 of the low dose female mice, and 7/50 of the high dose female mice.

Kidney Effects in Mice: Renal tubular cell karyomegaly was found in both male and female mice in dose-related incidences (male: control, 4/49; low dose, 17/49; high dose, 46/50; female: control, 0/48; low dose, 16/49; high dose, 38/50). This change is identical to that noted during the 13-week studies and in the 2-year rat studies. It was not, however, accompanied by proliferative changes (such as tubular epithelial cell hyperplasia) as it was in rats. One of 49 low dose male mice exhibited a renal tubular cell adenocarcinoma.

Pulmonary Effects in Mice: Acute passive congestion was diagnosed in from 10% to 20% of dosed males and females and in 2% of the chamber controls, but there were no increases in the incidences of proliferative lesions of the respiratory system in mice.

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Conclusions: Under the conditions of these inhalation studies, there was some evidence of carcinogenicity* of tetrachloroethylene in F344/N rats as shown by increased incidences of mononuclear cell leukemia in males and females and rare renal tubular cell neoplasms in males. There was clear evidence of carcinogenicity in B6C3F$_1$ mice as shown by increased incidences of both hepatocellular adenomas and carcinomas in males and of hepatocellular carcinomas in females.

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*Categories of evidence of carcinogenicity are defined in Note to Reader on page 2.

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SUMMARY OF THE INCIDENCE

OF

NEOPLASTIC AND NONNEOPLASTIC LESIONS

IN RATS AND MICE ADMINISTERED

TETRACHLOROETHYLENE

BY INHALATION FOR TWO YEARS

APPENDIXES A-D

Based on CBDS Tables Dated

February 1985 (Rats)
January 1985 (Mice)

Prepared for Board Draft 8/85

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLROETHYLENE

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)	1 (2%)	
Squamous cell carcinoma	1 (2%)		
Basal cell tumor			1 (2%)
Basal cell carcinoma			1 (2%)
Keratoacanthoma	3 (6%)	1 (2%)	
*Subcut tissue	(50)	(50)	(50)
Fibroma	3 (6%)	1 (2%)	4 (8%)
Fibrosarcoma		1 (2%)	
Neurilemoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(47)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma		1 (2%)	
Nephroblastoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	27 (54%)	36 (72%)	37 (74%)
#Spleen	(50)	(50)	(49)
Leukemia, mononuclear cell		1 (2%)	
#Liver	(50)	(50)	(49)
Leukemia, mononuclear cell	1 (2%)		
CIRCULATORY SYSTEM			
#Kidney	(49)	(49)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
Squamous cell carcinoma			1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
#Liver	(50)	(50)	(49)
Neoplastic nodule	4 (8%)	7 (14%)	4 (8%)
Hepatocellular carcinoma		1 (2%)	1 (2%)
#Jejunum	(42)	(47)	(47)
Leiomyoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Tubular cell adenoma	1 (2%)	3 (6%)	2 (4%)
Tubular cell adenocarcinoma			2 (4%)
Lipoma		1 (2%)	
Nephroblastoma		1 (2%)	
#Urinary bladder	(46)	(48)	(48)
Transitional cell papilloma	1 (2%)		

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(47)	(48)
Carcinoma, NOS	3 (6%)	2 (4%)	2 (4%)
Adenoma, NOS	17 (36%)	12 (26%)	16 (33%)
#Adrenal	(49)	(49)	(49)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(49)	(49)	(49)
Pheochromocytoma	22 (45%)	21 (43%)	23 (47%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(47)	(48)	(46)
Follicular cell carcinoma			1 (2%)
C-cell adenoma	3 (6%)	3 (6%)	4 (9%)
C-cell carcinoma	4 (9%)	6 (13%)	
#Parathyroid	(39)	(25)	(34)
Adenoma, NOS			2 (6%)
#Pancreatic islets	(43)	(46)	(46)
Islet cell adenoma	3 (7%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	2 (4%)	3 (6%)
Adenoma, NOS	1 (2%)	3 (6%)	3 (6%)
#Testis	(50)	(49)	(50)
Adenocarcinoma, NOS	1 (2%)		
Interstitial cell tumor	35 (70%)	39 (80%)	41 (82%)
*Epididymis	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		1 (2%)
Glioma, NOS	1 (2%)		4 (8%)
SPECIAL SENSE ORGANS			
*Eyelid	(50)	(50)	(50)
Sebaceous adenocarcinoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)	1 (2%)	2 (4%)
Mesothelioma, malignant	1 (2%)		1 (2%)

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Tubular cell adenocarcinoma, invasive			1 (2%)
Chordoma	1 (2%)		
Foot			
Sebaceous adenoma		1	

# Number of animals with tissue examined microscopically

* Number of animals necropsied

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	5	3
Moribund sacrifice	18	26	36
Terminal sacrifice	23	19	11
TUMOR SUMMARY			
Total animals with primary tumors**	50	48	50
Total primary tumors	146	151	163
Total animals with benign tumors	45	42	47
Total benign tumors	96	92	101
Total animals with malignant tumors	36	41	42
Total malignant tumors	45	51	56
Total animals with secondary tumors##	1	2	2
Total secondary tumors	1	2	2
Total animals with tumors uncertain-- benign or malignant	4	7	5
Total uncertain tumors	5	8	6

** Primary tumors: all tumors except secondary tumors

## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

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TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)
Keratoacanthoma		1 (2%)	
*Subcut tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Neurilemoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(49)
Alveolar/bronchiolar adenoma			1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		
C-cell carcinoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	18 (36%)	29 (58%)	28 (56%)
#Spleen	(50)	(49)	(49)
Leukemia, mononuclear cell		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
#Liver	(50)	(50)	(49)
Neoplastic nodule	2 (4%)		2 (4%)
URINARY SYSTEM			
#Urinary bladder	(47)	(44)	(46)
Transitional cell papilloma			1 (2%)
Granular cell tumor, malignant			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(48)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(50)	(48)	(50)
Carcinoma, NOS	4 (8%)	2 (4%)	3 (6%)
Adenoma, NOS	19 (38%)	21 (44%)	20 (40%)
#Adrenal	(50)	(49)	(47)
Cortical adenoma	2 (4%)	1 (2%)	2 (4%)
#Adrenal medulla	(50)	(49)	(47)
Pheochromocytoma	1 (2%)		2 (4%)
Pheochromocytoma, malignant			1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(46)	(48)	(46)
Follicular cell adenoma			1 (2%)
C-cell adenoma	3 (7%)	1 (2%)	3 (7%)
C-cell carcinoma	1 (2%)	4 (8%)	1 (2%)
#Parathyroid	(27)	(27)	(34)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(50)	(47)	(46)
Islet cell adenoma	1 (2%)		1 (2%)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	2 (4%)	2 (4%)	
Fibroadenoma	7 (14%)	3 (6%)	6 (12%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	3 (6%)	2 (4%)
Adenoma, NOS	3 (6%)	1 (2%)	2 (4%)
#Uterus	(49)	(49)	(50)
Fibroma	1 (2%)		
Leiomyosarcoma		1 (2%)	
Endometrial stromal polyp	5 (10%)	7 (14%)	7 (14%)
Endometrial stromal sarcoma		2 (4%)	1 (2%)
#Uterus/endometrium	(49)	(49)	(50)
Deciduoma		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive		2 (4%)	
Glioma, NOS	1 (2%)		2 (4%)
SPECIAL SENSE ORGANS			
*Eyelid	(50)	(50)	(50)
Neurofibroma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Odontoma, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
*Peritoneal cavity	(50)	(50)	(50)
Granular cell tumor, invasive			1 (2%)
ALL OTHER SYSTEMS			
Tail			
Neurofibrosarcoma	1		

# Number of animals with tissue examined microscopically

* Number of animals necropsied

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	5	5
Moribund sacrifice	21	24	21
Terminal sacrifice	23	21	24
TUMOR SUMMARY			
Total animals with primary tumors**	42	45	45
Total primary tumors	82	81	94
Total animals with benign tumors	32	30	32
Total benign tumors	45	37	50
Total animals with malignant tumors	30	39	38
Total malignant tumors	34	44	42
Total animals with secondary tumors##	1	3	1
Total secondary tumors	1	3	1
Total animals with tumors uncertain--benign or malignant	3		2
Total uncertain tumors	3		2

** Primary tumors: all tumors except secondary tumors

## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

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TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: CHAMBER CONTROL

ANIMAL NUMBER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WEEKS ON STUDY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Squamous cell carcinoma												X													
Keratoacanthoma								X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X					X			X	
Neurilemoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma														X											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Leukemia, mononuclear cell																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Hemangioma																								X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																	X	X							
Adenoma, NOS									X	X	X				X					X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma								X			X		X	X	X		X			X		X	X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																	X								
C-cell carcinoma																									X
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	N	N	N	+	N	+	N	+	+	+	+	+	N	+	+	N	N	N	N	+	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Interstitial cell tumor		X	X	X			X			X	X	X	X	X	X	X	X							X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																		X							
Glioma, NOS																									
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sebaceous adenocarcinoma																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma							X																		
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Mesothelioma, malignant		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chordoma																				X					
Leukemia, mononuclear cell	X		X	X	X	X		X	X		X		X	X	X	X	X	X			X	X			X

+	Tissue Examined Microscopically		No Tissue Information Submitted
-	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

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TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	026	038	004	005	006	007	008	010	011	014	015	017	019	021	022	024	027	031	033	034	035	036	041	043	050	
WEEKS ON STUDY	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	**TOTAL: TISSUES TUMORS**
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																		X								2
Squamous cell carcinoma																										1
Keratoacanthoma	X																					X				3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										3
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	-	-	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X						X			X				X				4
Leukemia, mononuclear cell																				X						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Esophagus	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																				X						1
Hemangioma																										1
Urinary bladder	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Transitional cell papilloma																	X									1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS	X																									3
Adenoma, NOS					X			X		X						X	X		X	X						17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																		X								1
Pheochromocytoma	X		X		X	X			X	X	X			X	X		X	X	X			X				22
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma																	X							X		3
C-cell carcinoma					X	X														X						4
Parathyroid	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	39
Pancreatic islets	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Islet cell adenoma			X									X								X						3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	+	+	N	+	+	N	+	+	N	N	+	+	+	N	+	N	N	N	N	+	*50
Fibroadenoma																X										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS				X																						1
Interstitial cell tumor		X	X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	35
Prostate	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X																	X								2
Adenoma, NOS																				X						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Glioma, NOS											X															1
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sebaceous adenocarcinoma																	X									1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS															X											1
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Chordoma																										1
Leukemia, mononuclear cell	X	X	X	X	X									X				X				X	X	X		27

* Animals Necropsied

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TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WEEKS ON STUDY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
Fibrosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																X									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Nephroblastoma, metastatic	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																X									
Hepatocellular carcinoma																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																X								X	
Lipoma																									
Nephroblastoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X															
Adenoma, NOS																			X		X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X					X	X		X				X				X	X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									X
C-cell carcinoma																			X	X					
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	N	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								X	X			X	X	X	X	X	X	X	X	X		X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Adenoma, NOS																						X			
BODY CAVITIES																									
Tunica vaginalis	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Foot, NOS																									
Sebaceous adenoma																									

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TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	018	005	033	049	008	004	007	011	012	016	017	020	022	024	025	026	034	035	037	038	041	043	046	047	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	101	102	102	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																		X								1
Keratoacanthoma																					X					1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma					X																					1
Nephroblastoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell												X														1
Lymph nodes	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	3[illegible]
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma						X																				1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule					X			X				X					X				X	X				7
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma																		X								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma												X														3
Lipoma														X												1
Nephroblastoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																X										2
Adenoma, NOS					X		X		X		X	X			X			X		X		X		X		12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X			X		X	X	X		X		X		X	X	X		X			X		X		X	21
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma			X												X											3
C-cell carcinoma					X	X												X				X				6
Parathyroid	-	-	+	+	-	-	+	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma																						X				2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	N	+	+	+	N	+	N	+	+	+	+	N	+	+	+	N	+	+	+	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	45
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																					X	X				2
Adenoma, NOS		X																X								3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X	X	X	X			X	X				X						X	X	X	X	X	X	X	36
Foot, NOS																										
Sebaceous adenoma																									X	[illegible]

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WEEKS ON STUDY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Basal cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Trachea	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Spleen	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Lymph nodes	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	-	-	+	-	+	-	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Squamous cell carcinoma				X																					
Salivary gland	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma								X																	
Bile duct	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS												X													
Adenoma, NOS		X			X			X			X				X		X	X						X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X		X					X		X		X	X	X				X		X		
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	-	N	-	N	N	N	N	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X			X	X	X		X	X	X	X			X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
Adenoma, NOS																									X
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Glioma, NOS																X					X				
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																	X								
Mesothelioma, malignant																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Tubular cell adenocarcinoma, invasive										X															
Leukemia, mononuclear cell	X		X	X	X	X	X	X	X		X			X	X		X	X		X	X	X	X	X	X

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TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE
(Continued)

ANIMAL NUMBER	023	034	028	050	004	018	017	027	029	032	033	037	047	002	005	008	009	015	022	024	030	035	038	041	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	098	098	100	100	102	102	102	102	102	102	102	102	103	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Basal cell tumor															X											1
Basal cell carcinoma											X															1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Fibroma								X							X						X					4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	48
Thymus	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	-	-	-	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma			X			X																				2
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	[illegible]
Neoplastic nodule													X						X				X		X	4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma												X												X		2
Tubular cell adenocarcinoma																						X				2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS											X															2
Adenoma, NOS		X		X		X	X	X	X	X											X					16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma		X				X	X			X	X		X	X	X		X	X	X	X					X	23
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell carcinoma				X																						1
C-cell adenoma												X	X			X						X				4
Parathyroid	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	-	34
Adenoma, NOS																X										2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	-	-	+	N	+	N	+	+	+	+	+	N	+	+	+	+	N	N	+	+	N	+	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS							X									X										3
Adenoma, NOS																					X	X				3
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																							X			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive											X															1
Glioma, NOS												X	X													4
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																									X	2
Mesothelioma, malignant												X														1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Tubular cell adenocarcinoma, invasive																										1
Leukemia, mononuclear cell	X	X	X	X	X		X	X				X	X	X		X	X	X	X	X		X	X		X	37

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: CHAMBER CONTROL

ANIMAL NUMBER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WEEKS ON STUDY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																		X							
Neurilemoma, malignant							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X									X					X			
Adenoma, NOS	X						X					X	X			X		X			X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X											X
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma									X												X				
C-cell carcinoma																									X
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																							X		
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma								X	X	X		X													
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
Adenoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Endometrial stromal polyp															X				X		X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurofibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Odontoma, NOS											X														
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell						X								X	X	X			X	X	X			X	
Tail																									
Neurofibrosarcoma																									

+	Tissue Examined Microscopically		No Tissue Information Submitted
-	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

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TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	033	049	002	003	004	005	007	010	012	016	017	022	023	025	026	027	028	030	034	038	039	040	044	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	-	+	+	+	+	+	N	+	+	*50
Squamous cell papilloma						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	*50
Sarcoma, NOS																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	-	-	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																	X		X							2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																		X		X						5
Adenoma, NOS	X	X				X					X	X	X				X				X	X	X		X	20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										2
Pheochromocytoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	46
C-cell adenoma	X																									3
C-cell carcinoma																										1
Parathyroid	+	-	+	+	-	-	+	+	+	-	-	+	-	-	-	+	+	-	+	-	-	-	+	-	+	27
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
Islet cell carcinoma										X																1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	*50
Adenocarcinoma, NOS						X												X								2
Fibroadenoma																		X			X				X	7
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															2
Adenoma, NOS														X										X		3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma												X														1
Endometrial stromal polyp																X		X								5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS														X												1
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurofibroma																X										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Odontoma, NOS																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar ca, invasive												X														1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X		X	X		X							X				X	X	X		X				X	18
Tail																										
Neurofibrosarcoma										X																1

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	005
WEEKS ON STUDY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	101
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS												X								X					
Adenoma, NOS	X			X		X			X		X		X			X	X	X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																	X					X			
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Adenocarcinoma, NOS		X											X												
Fibroadenoma																	X	X							
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X		X														
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Endometrial stromal polyp									X			X							X						
Endometrial stromal sarcoma														X											
Deciduoma									X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive												X								X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X		X	X	X	X	X	X	X	X					X		X	X	X			X	X		X

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	040	045	010	018	001	003	008	009	011	012	013	015	019	023	030	031	034	037	038	039	043	044	046	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	101	102	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Squamous cell papilloma																		X								1
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell											X															1
Lymph nodes	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										2
Adenoma, NOS			X	X	X	X	X	X		X							X	X		X			X		X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma																					X					1
C-cell carcinoma						X																			X	4
Parathyroid	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	-	-	+	+	-	27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Adenocarcinoma, NOS																										2
Fibroadenoma																					X					3
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS												X														3
Adenoma, NOS									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Endometrial stromal polyp	X	X										X								X						7
Endometrial stromal sarcoma																					X					2
Deciduoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X	X	X	X		X	X	X	X					X	X						X			X	29

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	014	034	004	047	002	023	015	029	040	013	022	024	050	014	012	037	005	039	025	045	002	010	013	009	005
WEEKS ON STUDY	075	076	077	077	078	078	081	082	085	086	086	088	088	089	090	090	095	095	099	099	100	100	100	101	102
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Squamous cell carcinoma		X																							
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Granular cell tumor, malignant																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS									X																
Adenoma, NOS		X	X											X	X						X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								X	
Pheochromocytoma																	X								
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																X									
C-cell adenoma														X					X						
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									X
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Fibroadenoma											X												X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp													X	X					X						
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS	X				X																				
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Granular cell tumor, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X	X			X	X	X		X		X	X	X	X	X	X	X	X	X		X		X	X

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TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE
(Continued)

ANIMAL NUMBER	033	001	004	007	011	016	017	020	021	023	026	027	028	030	031	032	034	035	041	042	043	044	046	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																			X							1
Lymph nodes	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	45
Thymus	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																		X								1
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule					X							X														2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
Esophagus	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Transitional cell papilloma				X																						1
Granular cell tumor, malignant				X																						1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS					X																					3
Adenoma, NOS	X		X	X		X		X			X	X	X				X	X	X	X		X				20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma																				X						2
Pheochromocytoma						X																				2
Pheochromocytoma, malignant																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																										1
C-cell adenoma			X																							3
C-cell carcinoma												X														1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	-	[illegible]	-	-	+	+	+	+	-	+	+	+	+	34
Adenoma, NOS																										1
Pancreatic islets	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
Islet cell adenoma									X																	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Fibroadenoma												X							X							6
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X											X									2
Adenoma, NOS												X		X												2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																X		X		X			X			7
Endometrial stromal sarcoma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										2
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	*50
Carcinoma, NOS																					X					1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Granular cell tumor, invasive				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X		X	X			X	X	X				X		X					X			X			28

*Animals Necropsied

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APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Multiple organs	(49)	(50)	(50)
Fibrous histiocytoma, malignant			1 (2%)
*Subcut tissue	(49)	(50)	(50)
Sebaceous adenoma	1 (2%)	1 (2%)	
#Spleen	(49)	(48)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
#Liver	(49)	(49)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(49)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	7 (14%)	1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	1 (2%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)	7 (14%)	1 (2%)
*Subcut tissue	(49)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)		
#Spleen	(49)	(48)	(50)
Sarcoma, NOS			1 (2%)
Malignant lymphoma, NOS			1 (2%)
#Mesenteric lymph node	(25)	(24)	(27)
Malignant lymphoma, NOS			1 (4%)
#Stomach wall	(48)	(44)	(49)
Mast cell tumor	1 (2%)		
*Preputial gland	(49)	(50)	(50)
Mast cell tumor			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(49)	(50)	(50)
Hemangioma		1 (2%)	
*Pulmonary artery	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
*Pulmonary vein	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	1 (2%)
#Liver	(49)	(49)	(50)
Hemangioma	2 (4%)	2 (4%)	2 (4%)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(49)	(49)	(50)
Hepatocellular adenoma	11 (22%)	8 (16%)	18 (36%)
Hepatocellular carcinoma	7 (14%)	25 (51%)	26 (52%)
#Ileum	(49)	(42)	(45)
Adenocarcinoma, NOS	2 (4%)		
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Tubular cell adenocarcinoma		1 (2%)	

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary	(47)	(41)	(44)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS		1 (2%)	
#Adrenal	(49)	(48)	(49)
Cortical adenoma	2 (4%)	1 (2%)	1 (2%)
#Adrenal medulla	(49)	(48)	(49)
Pheochromocytoma		1 (2%)	
#Thyroid	(47)	(46)	(50)
Follicular cell adenoma			1 (2%)
C-cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(49)	(48)	(49)
Interstitial cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(50)
Papillary adenoma		1 (2%)	
Papillary cystadenocarcinoma NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	

# Number of animals with tissue examined microscopically
* Number of animals necropsied

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	18	7
Moribund sacrifice		7	11
Terminal sacrifice	46	25	32
Animal missexed	1		

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	28	38	42
Total primary tumors	42	56	60
Total animals with benign tumors	18	16	21
Total benign tumors	20	21	23
Total animals with malignant tumors	17	32	30
Total malignant tumors	21	35	36
Total animals with secondary tumors ##	2	10	2
Total secondary tumors	2	10	2
Total animals with tumors uncertain-- benign or malignant	1		1
Total uncertain tumors	1		1

** Primary tumors: all tumors except secondary tumors

Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

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TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Multiple organs	(49)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
*Skin	(49)	(50)	(50)
Squamous cell papilloma			1 (2%)
*Subcut tissue	(49)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(48)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Hepatocellular carcinoma, metastatic		2 (4%)	7 (14%)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)
Sarcoma, NOS, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, NOS	8 (16%)	10 (20%)	7 (14%)
Malig. lymphoma, histiocytic type		1 (2%)	
#Spleen	(49)	(49)	(50)
Thymoma, metastatic	1 (2%)		
Malignant lymphoma, NOS		1 (2%)	1 (2%)
#Bronchial lymph node	(34)	(31)	(26)
Adenocarcinoma, NOS, metastatic			1 (4%)
Alveolar/bronchiolar carcinoma, metastatic			1 (4%)
#Ileum	(48)	(45)	(46)
Malignant lymphoma, NOS		1 (2%)	
#Thymus	(35)	(39)	(22)
Thymoma, malignant	1 (3%)		
CIRCULATORY SYSTEM			
*Eye	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Spleen	(49)	(49)	(50)
Hemangioma		1 (2%)	
#Mesenteric lymph node	(34)	(31)	(26)
Hemangioma			1 (4%)
#Heart	(48)	(50)	(50)
Sarcoma, NOS			1 (2%)
*Pulmonary artery	(49)	(50)	(50)
Fibrous histiocytoma, metastatic	1 (2%)		
#Liver	(48)	(50)	(50)
Hemangiosarcoma		3 (6%)	
#Ovary	(48)	(49)	(43)
Hemangioma	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver	(48)	(50)	(50)
Hepatocellular adenoma	3 (6%)	6 (12%)	2 (4%)
Hepatocellular carcinoma	1 (2%)	13 (26%)	36 (72%)
#Forestomach	(48)	(50)	(48)
Papilloma, NOS	1 (2%)		
*Rectum	(49)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary	(45)	(43)	(42)
Carcinoma, NOS	5 (11%)	3 (7%)	3 (7%)
Adenoma, NOS	2 (4%)		1 (2%)
Chromophobe adenoma			1 (2%)
#Adrenal medulla	(47)	(49)	(49)
Carcinoma, NOS			1 (2%)
Adenoma, NOS		1 (2%)	
Pheochromocytoma		1 (2%)	
#Periadrenal tissue	(47)	(49)	(49)
Fibrosarcoma, metastatic	1 (2%)		
#Thyroid	(48)	(48)	(48)
Follicular cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	1 (2%)
Adenosquamous carcinoma		1 (2%)	1 (2%)
Fibrosarcoma	1 (2%)		
#Uterus	(43)	(44)	(48)
Leiomyoma		1 (2%)	
Leiomyosarcoma	1 (2%)	1 (2%)	
Endometrial stromal polyp	1 (2%)		
#Ovary	(48)	(49)	(43)
Papillary cystadenoma, NOS		1 (2%)	
Fibrous histiocytoma, metastatic	1 (2%)		
Mesothelioma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain	(48)	(49)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Sebaceous adenoma			1 (2%)
*Harderian gland	(49)	(50)	(50)
Papillary carcinoma			1 (2%)
Adenoma, NOS	1 (2%)		1 (2%)
Papillary adenoma		1 (2%)	1 (2%)
*Ear	(49)	(50)	(50)
Squamous cell papilloma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			

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TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Fibrosarcoma, metastatic	1 (2%)		
*Peritoneal cavity	(49)	(50)	(50)
Hepatocellular carcinoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Carcinosarcoma	1 (2%)		

Number of animals with tissue examined microscopically
* Number of animals necropsied

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	10	11
Moribund sacrifice	8	7	21
Terminal sacrifice	36	31	17
Accidentally killed, NOS	2	2	1
Animal missexed	1		
TUMOR SUMMARY			
Total animals with primary tumors**	27	35	43
Total primary tumors	38	52	64
Total animals with benign tumors	13	14	10
Total benign tumors	14	15	10
Total animals with malignant tumors	22	31	41
Total malignant tumors	24	36	54
Total animals with secondary tumors##	4	2	8
Total secondary tumors	6	2	12
Total animals with tumors uncertain-- benign or malignant		1	
Total uncertain tumors		1	

** Primary tumors: all tumors except secondary tumors
## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: CHAMBER CONTROL

ANIMAL NUMBER	007	044	034	040	001	002	003	004	005	006	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022
WEEKS ON STUDY	099	097	098	098	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma														X											
Malignant lymphoma, NOS						X											X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic								X																	
Alveolar/bronchiolar adenoma					X																X				
Alveolar/bronchiolar carcinoma					X		X																		
Trachea	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, malignant																					X				
Lymph nodes	S	-	-	+	-	+	-	-	+	+	+	+	+	-	+	+	+	-	-	-	-	+	+	+	+
Thymus	S	-	-	+	-	+	+	+	-	-	-	+	-	-	+	+	+	-	+	+	-	+	+	-	+
CIRCULATORY SYSTEM																									
Heart	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X		X		X									X				X		X	X
Hepatocellular carcinoma				X				X	X																
Fibrous histiocytoma, malignant																					X				
Hemangioma																									
Hemangiosarcoma																				X					
Bile duct	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	S	N	+	N	+	N	+	+	N	+	N	+	+	+	+	N	+	N	N	N	N	+	+	+	+
Pancreas	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Stomach	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
Mast cell tumor																									
Small intestine	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Large intestine	S	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	S	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	S	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma												X								X					
Thyroid	S	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+	-
C-cell carcinoma																								X	
Parathyroid	S	+	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+	-	+	-	-	+	-
REPRODUCTIVE SYSTEM																									
Mammary gland	S	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N
Testis	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X																
Prostate	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenocarcinoma, NOS									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									

+ : Tissue Examined Microscopically
- : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed

: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	023	024	025	026	027	028	029	030	031	032	033	035	036	037	038	039	041	042	043	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*49
Sebaceous adenoma																										1
Malignant lymphoma, NOS																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic												X														2
Alveolar/bronchiolar adenoma																							X			3
Alveolar/bronchiolar carcinoma			X																		X					4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, malignant																										1
Lymph nodes	+	-	+	-	-	-	-	-	+	-	+	+	-	-	-	-	+	+	+	+	-	-	+	+	+	25
Thymus	-	+	-	-	-	-	+	+	-	+	-	+	+	-	+	-	+	+	-	+	-	+	-	-	+	25
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma								X			X							X							X	11
Hepatocellular carcinoma				X								X												X	X	[illegible]
Fibrous histiocytoma, malignant																										1
Hemangioma										X						X										2
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	+	+	+	+	N	N	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mast cell tumor																			X							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																							X			2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										2
Thyroid	+	+	+	+	+	-	-	+	[illegible]	[illegible]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell carcinoma																										1
Parathyroid	-	+	-	-	+	+	-	+	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Papillary cystadenocarcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, NOS												X														1

* Animals Necropsied

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	002	043	007	005	031	012	003	045	009	030	041	020	025	019	047	026	038	025	039	046	008	011	034	023	016
WEEKS ON STUDY	046	055	061	063	066	074	075	079	085	085	085	086	086	089	089	092	092	096	096	097	098	098	098	099	102
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic					X				X				X	X									X		
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma																									
Trachea	+	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	A	-	+	-	-	-	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	+	-
Thymus	+	-	A	+	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	+	+	-
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																		X							X
DIGESTIVE SYSTEM																									
Salivary gland	+	+	A	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Hepatocellular carcinoma				X	X	X	X		X		X		X	X	X	X		X	X	X	X	X	X		X
Hemangioma																									X
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	N	N	N	N	N	-	+	+	N	N	N	-	-	N	N	N	+	-	N	+	+
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Stomach	+	+	A	-	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+
Small intestine	-	-	A	-	+	-	-	-	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+
Large intestine	+	-	A	-	+	-	-	+	+	-	+	+	+	+	+	-	-	-	-	+	+	+	+	-	+
URINARY SYSTEM																									
Kidney	+	-	A	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	A	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	-	-	+
ENDOCRINE SYSTEM																									
Pituitary	+	-	A	+	+	+	-	+	-	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS					X																				
Adrenal	+	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									X
Thyroid	-	+	A	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	-	-	A	-	-	-	-	-	-	+	-	+	+	-	+	-	-	+	+	+	-	-	-	+	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	A	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																						X			
Malignant lymphoma, NOS		X								X					X								X	X	

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE
(Continued)

ANIMAL NUMBER	001	004	006	010	013	014	015	017	019	021	022	024	027	029	032	033	035	036	037	040	042	044	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																			X	X						7
Alveolar/bronchiolar adenoma			X	X										X	X											5
Alveolar/bronchiolar carcinoma																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	-	-	-	-	+	-	-	-	-	+	+	+	-	+	+	+	-	+	-	-	+	+	+	-	24
Thymus	+	-	-	+	+	-	-	+	-	+	-	-	-	-	-	-	+	+	+	-	+	+	-	+	+	18
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										[illegible]
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X		X								X					X		X	X					X		8
Hepatocellular carcinoma						X	X		X	X			X		X				X	X						25
Hemangioma														X												2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	-	+	N	+	+	N	+	+	+	N	+	+	+	N	-	N	-	+	N	+	-	+	+	-	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	49
Tubular cell adenocarcinoma					X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	41
Carcinoma, NOS																										1
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma					X																					1
Pheochromocytoma																										1
Thyroid	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	46
Parathyroid	-	+	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	15
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																					X					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
Malignant lymphoma, NOS	X																							X		7

* Animals Necropsied

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	037	025	001	005	008	014	026	018	013	011	020	038	050	048	044	045	024	036	002	003	004	006	007	009	010
WEEKS ON STUDY	060	062	073	073	074	077	079	080	083	085	089	093	094	095	097	100	103	103	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic															X										
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X																	
Malignant lymphoma, NOS																						X			
Lymph nodes	-	-	-	-	-	-	+	+	+	-	+	+	-	+	-	[illegible]	+	+	-	-	+	+	-	+	+
Malignant lymphoma, NOS																									
Thymus	-	-	-	-	-	-	-	-	-	-	-	+	+	-	+	-	+	-	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	[illegible]	+	+	+	-	+	+	+	+	+
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																		X							
DIGESTIVE SYSTEM																									
Salivary gland	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	-	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X													X			X			X			
Hepatocellular carcinoma	X			X	X		X	X	X	X		X	X		X		X	X		X	X			X	
Hemangioma																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	N	+	N	+	N	N	N	+	N	N	-	N	N	N	+	-	+	+	+	+
Pancreas	+	-	+	+	+	-	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Esophagus	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	-	-	+	-	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	-	+	-	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	-	+	-	-	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Follicular cell adenoma			X																						
Parathyroid	-	-	+	-	+	+	[illegible]	+	+	-	+	+	[illegible]	+	+	+	-	-	+	-	-	-	-	-	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	-	-	+	+	-	+	+	-	-	+
Prostate	-	+	+	-	-	-	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	-	-	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mast cell tumor			X																						
NERVOUS SYSTEM																									
Brain	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenocarcinoma, NOS																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, malignant		X																							
Malignant lymphoma, NOS																									

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TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE
(Continued)

ANIMAL NUMBER	012	015	016	017	019	021	022	023	027	028	029	030	031	032	033	034	035	039	040	041	042	043	046	047	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																			X							1
Alveolar/bronchiolar carcinoma		X									X										X					4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Malignant lymphoma, NOS																										1
Lymph nodes	+	+	-	+	-	+	+	-	-	-	-	-	+	-	+	+	+	-	-	+	+	+	+	+	-	27
Malignant lymphoma, NOS																						X				1
Thymus	+	+	-	-	+	+	-	+	-	+	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X	X		X	X			X	X	X	X	X			X	X	X		X	X	18
Hepatocellular carcinoma	X	X						X				X				X	X	X	X		X	X	X			26
Hemangioma																		X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	N	+	+	+	N	N	N	N	+	+	+	+	+	N	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	44
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	-	+	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	+	21
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mast cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary cystadenocarcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, malignant																										1
Malignant lymphoma, NOS																					X					1

*Animals Necropsied

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TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: CHAMBER CONTROL

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ANIMAL NUMBER	041	022	049	018	038	040	007	016	032	048	023	024	025	034	001	002	003	004	005	006	008	009	010	011	012
WEEKS ON STUDY	003	004	016	058	060	072	086	093	096	097	099	099	099	099	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	S	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma, metastatic																						X			
Lymph nodes	+	+	-	S	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+
Thymus	+	+	-	S	+	-	-	-	+	+	+	-	-	+	+	+	+	-	+	-	+	+	+	-	+
Thymoma, malignant																						X			
CIRCULATORY SYSTEM																									
Heart	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessels	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	S	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X			X													
Hepatocellular carcinoma																									
Bile duct	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	S	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	-	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Stomach	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																				X					
Small intestine	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	S	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	-	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																				X					
Adenoma, NOS										X															
Adrenal	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic													X												
Thyroid	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	S	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	S	+	+	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Fibrosarcoma													X												
Uterus	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																	X								
Ovary	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic																									
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	S	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
SPECIAL SENSE ORGANS																									
Eye	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
Harderian gland	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
Ear	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
BODY CAVITIES																									
Mediastinum	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, malignant												X													
Carcinosarcoma							X																		
Malignant lymphoma, NOS								X	X	X	X														

+	Tissue Examined Microscopically		:	No Tissue Information Submitted
-	Required Tissue Not Examined Microscopically	C	:	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	:	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	:	Animal Missing
S	Animal Missexed	B	:	No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	013	014	015	017	019	020	021	026	027	028	029	030	031	033	035	036	037	039	042	043	044	045	046	047	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*49
Fibrous histiocytoma, malignant			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma										X		X												X	X	4
Alveolar/bronchiolar carcinoma																X			X							2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma, metastatic																										1
Lymph nodes	-	+	-	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	-	-	-	-	+	-	+	34
Thymus	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	35
Thymoma, malignant																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrous histiocytoma, metastatic			X																							1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma																	X									5
Hepatocellular carcinoma													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	*49
Squamous cell carcinoma					X																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	45
Carcinoma, NOS						X			X						X									X		5
Adenoma, NOS																					X					2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	47
Fibrosarcoma, metastatic																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	-	-	-	-	-	+	+	+	-	-	-	-	-	-	+	+	+	-	+	+	-	-	-	-	-	18
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	+	+	N	+	N	N	+	+	N	N	+	+	+	+	N	+	+	+	*49
Fibrosarcoma																										1
Uterus	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	43
Leiomyosarcoma										X																1
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrous histiocytoma, metastatic			X																							1
Hemangioma					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS, metastatic																								X		1
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Hemangiosarcoma					X																					1
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS																										1
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	*49
Squamous cell papilloma																X										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrous histiocytoma, malignant																										1
Carcinosarcoma																										1
Malignant lymphoma, NOS	X			X		X																	X			8

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: LOW DOSE

DRAFT

ANIMAL NUMBER	027	043	015	041	025	050	011	002	035	049	027	042	010	024	045	026	032	020	033	001	003	004	005	006	007
WEEKS ON STUDY	005	005	007	007	011	014	024	034	075	076	084	090	091	094	094	100	101	102	103	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
Alveolar/bronchiolar adenoma																		X			X				
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Malignant lymphoma, NOS																									
Lymph nodes	-	+	+	+	+	-	-	+	-	-	+	+	-	-	-	+	-	+	-	+	+	+	+	-	+
Thymus	+	-	+	-	+	+	+	-	-	-	+	+	+	-	-	+	+	+	+	-	+	+	+	-	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X		X				X	
Hepatocellular carcinoma										X				X	X	X		X							
Hemangiosarcoma																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	+	N	+	N	N	N	N	N	+	+	N	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	-	-	+	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																								X	
Large intestine	+	+	+	+	-	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+		-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	-	-	-	+	-	+	-	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Pheochromocytoma																									
Thyroid	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
Parathyroid	-	-	-	-	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	-	N	-	N	N	N	N	+	+	N	+	+	+	+	N	+	-	N	+	+	N	+
Adenocarcinoma, NOS																	X								
Adenosquamous carcinoma																									
Uterus	+	+	-	-	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
Leiomyoma													X												
Leiomyosarcoma																									
Ovary	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
Mesothelioma, NOS												X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS								X			X				X				X				X		X
Malig. lymphoma, histiocytic type													X												

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	008	009	012	013	014	016	017	018	019	021	022	023	028	029	030	031	034	036	038	039	040	044	046	047	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																			X							2
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																X										1
Malignant lymphoma, NOS																				X						1
Lymph nodes	-	+	-	-	-	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	31
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																X		X							[illegible]
Hepatocellular carcinoma		X			X				X	X	X					X		X	X							13
Hemangiosarcoma																X		X								3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	-	-	+	+	-	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	43
Carcinoma, NOS	X			X																		X				3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																										1
Pheochromocytoma																						X				1
Thyroid	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Parathyroid	-	-	-	-	+	-	-	+	-	+	-	+	+	+	-	-	-	+	-	-	-	-	-	-	+	17
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	*50
Adenocarcinoma, NOS																										1
Adenosquamous carcinoma								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	44
Leiomyoma																										1
Leiomyosarcoma					X																					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS																					X					1
Mesothelioma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																		X								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS							X					X	X					X								10
Malig. lymphoma, histiocytic type																										1

* Animals Necropsied

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TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	012	016	032	020	014	043	031	013	027	035	029	045	017	024	036	047	048	025	039	037	042	033	011	015	019
WEEKS ON STUDY	001	036	054	067	069	069	076	078	085	085	088	088	089	089	091	093	093	095	096	097	097	098	099	100	101
INTEGUMENTARY SYSTEM																									
Skin	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic						X																			
Hepatocellular carcinoma, metastatic				X																					
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma				X																					
Sarcoma, NOS, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	-	-	+	+	+	+	-	+	-	+	-	+	-	-	-	+	-	-	+	+	-	-	-	+	+
Adenocarcinoma, NOS, metastatic						X																			
Alveolar/bronchiolar ca, metastatic				X																					
Hemangioma																									
Thymus	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	+	-	+	-	-	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS				X																					
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X																	
Hepatocellular carcinoma				X	X		X			X	X	X	X	X	X		X	X	X	X			X	X	X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+
Gallbladder & common bile duct	+	N	+	-	N	N	N	-	-	N	N	-	N	-	N	N	+	+	N	-	N	-	N	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Large intestine	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
Pituitary	-	+	-	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
Carcinoma, NOS																									
Adenoma, NOS																							X		
Chromophobe adenoma											X														
Adrenal	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	-	-	-	+	+	-	+
Carcinoma, NOS																			X						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Parathyroid	+	-	+	+	+	-	+	+	-	-	+	+	-	+	-	+	+	+	-	-	-	+	+	+	-
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	-	N	+	+	+	N	N	+	N	+	N	+	+	N	N	+	+
Adenocarcinoma, NOS						X																			
Adenosquamous carcinoma									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	-	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sebaceous adenoma																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary carcinoma																									
Adenoma, NOS																									
Papillary adenoma																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, invasive				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS			X											X		X						X			

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	040	010	049	023	044	050	001	002	003	004	005	006	007	008	009	018	021	022	026	028	030	034	038	041	046	
WEEKS ON STUDY	101	102	102	103	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL: TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic				X	X												X		X		X				X	7
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																X										2
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																						X				1
Lymph nodes	+	-	-	-	+	+	-	+	-	+	-	+	+	-	+	-	+	+	+	-	+	+	+	-	-	28
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar ca, metastatic																										1
Hemangioma															X											1
Thymus	-	-	-	-	-	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	22
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									2
Hepatocellular carcinoma		X	X	X	X			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	36
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	N	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	42
Carcinoma, NOS		X						X							X											3
Adenoma, NOS																										1
Chromophobe adenoma																										1
Adrenal	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
Parathyroid	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	+	23
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	N	+	+	+	+	+	N	+	+	+	N	+	+	+	N	N	+	+	+	+	N	*50
Adenocarcinoma, NOS																										1
Adenosquamous carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	48
Ovary	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	43
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	+	N	N	N	N	N	*50
Sebaceous adenoma																				X						1
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary carcinoma																						X				1
Adenoma, NOS																	X									1
Papillary adenoma			X																							1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS															X	X				X						7

* Animals Necropsied

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APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
Abscess, NOS			1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, basal cell	1 (2%)		
Hyperkeratosis	1 (2%)		
Acanthosis			1 (2%)
Parakeratosis			1 (2%)
*Subcut tissue	(50)	(50)	(50)
Abscess, NOS			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS	2 (4%)	1 (2%)	1 (2%)
Mineralization	34 (68%)	35 (70%)	34 (68%)
Inflammation, NOS	11 (22%)	9 (18%)	7 (14%)
Inflammation, suppurative	10 (20%)	14 (28%)	11 (22%)
Hyperplasia, epithelial	5 (10%)	5 (10%)	5 (10%)
Metaplasia, squamous		5 (10%)	5 (10%)
*Larynx	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Inflammation, NOS		3 (6%)	2 (4%)
Inflammation, suppurative	9 (18%)	16 (32%)	7 (14%)
Hyperplasia, epithelial			1 (2%)
Metaplasia, squamous			2 (4%)
#Trachea	(48)	(48)	(49)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
#Lung/bronchiole	(50)	(47)	(50)
Inflammation, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		2 (4%)
#Lung	(50)	(47)	(50)
Foreign body, NOS		1 (2%)	
Congestion, NOS		1 (2%)	1 (2%)
Edema, NOS		1 (2%)	
Hemorrhage	4 (8%)	4 (9%)	4 (8%)
Inflammation, NOS			4 (8%)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, granulomatous focal	1 (2%)	2 (4%)	
Fibrosis	2 (4%)		7 (14%)
Perivascular cuffing			1 (2%)
Necrosis, NOS	1 (2%)		
Hyperplasia, alveolar epithelium	7 (14%)	3 (6%)	3 (6%)
Metaplasia, squamous	1 (2%)		
Metaplasia, osseous	2 (4%)	1 (2%)	
Histiocytosis	8 (16%)	7 (15%)	15 (30%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hematopoiesis			1 (2%)
#Bone marrow	(48)	(46)	(48)
Fibrosis			4 (8%)

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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Spleen	(50)	(50)	(49)
Fibrosis	6 (12%)	4 (8%)	4 (8%)
Necrosis, NOS		3 (6%)	1 (2%)
Hemosiderosis	1 (2%)		1 (2%)
Metaplasia, osseous	1 (2%)		
Hematopoiesis		1 (2%)	1 (2%)
#Mandibular lymph node	(46)	(44)	(46)
Hyperplasia, NOS	8 (17%)	10 (23%)	12 (26%)
#Thoracic lymph node	(46)	(44)	(46)
Hemosiderosis	1 (2%)		1 (2%)
Hyperplasia, NOS		1 (2%)	1 (2%)
#Lung	(50)	(47)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(50)	(49)
Leukocytosis, NOS	2 (4%)	1 (2%)	
Hematopoiesis			1 (2%)
#Colon	(41)	(44)	(45)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal	(49)	(49)	(49)
Hematopoiesis	2 (4%)	2 (4%)	
#Thymus	(35)	(34)	(31)
Degeneration, cystic		1 (3%)	
CIRCULATORY SYSTEM			
#Brain	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Mediastinum	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Splenic capsule	(50)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Mandibular lymph node	(46)	(44)	(46)
Lymphangiectasis	1 (2%)	1 (2%)	2 (4%)
*Nasal cavity	(50)	(50)	(50)
Thrombosis, NOS	9 (18%)	11 (22%)	19 (38%)
#Lung	(50)	(47)	(50)
Thrombosis, NOS	[illegible] (2%)	1 (2%)	2 (4%)
#Heart	(50)	(50)	(50)
Mineralization	1 (2%)		
Thrombosis, NOS	6 (12%)	4 (8%)	10 (20%)
Thrombus, organized	1 (2%)		
Inflammation, NOS	5 (10%)	7 (14%)	1 (2%)
Fibrosis	41 (82%)	32 (64%)	33 (66%)
Necrosis, NOS	[illegible] (2%)		1 (2%)
*Blood vessel	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Inflammation, chronic		3 (6%)	
Hypertrophy, NOS	1 (2%)	1 (2%)	3 (6%)
#Liver	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		1 (2%)
#Testis	(50)	(49)	(50)
Perivasculitis	2 (4%)		3 (6%)
DIGESTIVE SYSTEM			
*Oral mucosa	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	
Erosion			1 (2%)
Hyperplasia, epithelial			1 (2%)

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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
*Tongue	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Inflammation, granulomatous focal		1 (2%)	
Hyperplasia, epithelial			1 (2%)
*Tooth	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	1 (2%)		
#Salivary gland	(48)	(48)	(48)
Inflammation, NOS	1 (2%)	1 (2%)	
Metaplasia, squamous	1 (2%)	3 (6%)	2 (4%)
#Liver	(50)	(50)	(49)
Hemorrhage		1 (2%)	
Inflammation, suppurative	1 (2%)		
Inflammation, granulomatous focal	2 (4%)	2 (4%)	2 (4%)
Degeneration, NOS	6 (12%)	5 (10%)	9 (18%)
Degeneration, cystic	8 (16%)	7 (14%)	9 (18%)
Degeneration, lipoid	7 (14%)	3 (6%)	10 (20%)
Necrosis, NOS	4 (8%)	4 (8%)	4 (8%)
Basophilic cyto change	22 (44%)	19 (38%)	16 (33%)
Eosinophilic cyto change		1 (2%)	
Clear cell change	2 (4%)	2 (4%)	1 (2%)
Hepatocytomegaly	1 (2%)		
Angiectasis	3 (6%)	8 (16%)	4 (8%)
Regeneration, NOS		1 (2%)	
#Liver/periportal	(50)	(50)	(49)
Inflammation, NOS		1 (2%)	
Fibrosis		1 (2%)	
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	26 (52%)	36 (72%)	30 (61%)
#Pancreas	(43)	(46)	(46)
Inflammation, NOS			1 (2%)
Atrophy, focal	11 (26%)	5 (11%)	11 (24%)
Atrophy, diffuse	4 (9%)	4 (9%)	1 (2%)
#Pancreatic acinus	(43)	(46)	(46)
Focal cellular change	1 (2%)		
#Stomach	(48)	(49)	(49)
Ulcer, NOS		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Glandular stomach	(48)	(49)	(49)
Hemorrhage	1 (2%)		
Ulcer, NOS	1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	
Erosion		2 (4%)	
Degeneration, cystic	1 (2%)		
#Forestomach	(48)	(49)	(49)
Inflammation, NOS			4 (8%)
Ulcer, NOS		1 (2%)	5 (10%)
Inflammation, suppurative		1 (2%)	1 (2%)
Hyperplasia, epithelial	2 (4%)	2 (4%)	6 (12%)
#Small intestine	(42)	(47)	(47)
Inflammation, NOS	1 (2%)		
#Colon	(41)	(44)	(45)
Parasitism	10 (24%)	10 (23%)	4 (9%)
*Rectum	(50)	(50)	(50)
Parasitism	4 (8%)	5 (10%)	4 (8%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Cyst, NOS			1 (2%)
Nephropathy	48 (98%)	49 (100%)	50 (100%)
Infarct, NOS	1 (2%)		
Nuclear enlargement	1 (2%)	37 (76%)	47 (94%)
Hyperplasia, tubular cell		3 (6%)	5 (10%)
#Kidney/tubule	(49)	(49)	(50)
Mineralization		1 (2%)	1 (2%)
#Kidney/pelvis	(49)	(49)	(50)
Inflammation, suppurative		2 (4%)	
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(46)	(48)	(48)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative		1 (2%)	2 (4%)
Inflammation, granulomatous focal	1 (2%)		
Hyperplasia, epithelial		1 (2%)	2 (4%)
*Urethra	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(47)	(48)
Cyst, NOS	1 (2%)		
Degeneration, NOS			1 (2%)
Degeneration, cystic	4 (9%)	4 (9%)	8 (17%)
Pigmentation, NOS			1 (2%)
Hyperplasia, NOS	10 (21%)	10 (21%)	12 (25%)
#Adrenal	(49)	(49)	(49)
Congestion, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Degeneration, cystic			2 (4%)
Degeneration, lipoid	17 (35%)	6 (12%)	11 (22%)
Necrosis, NOS			1 (2%)
#Adrenal cortex	(49)	(49)	(49)
Hyperplasia, NOS	11 (22%)	5 (10%)	7 (14%)
#Adrenal medulla	(49)	(49)	(49)
Hyperplasia, NOS	5 (10%)	14 (29%)	12 (24%)
#Thyroid	(47)	(48)	(46)
Cyst, NOS		1 (2%)	
Degeneration, cystic	7 (15%)	3 (6%)	2 (4%)
Hyperplasia, C-cell	11 (23%)	8 (17%)	5 (11%)
Hyperplasia, follicular cell			1 (2%)
#Parathyroid	(3[illegible])	(35)	(34)
Hyperplasia, NOS	2 (5%)	1 (3%)	2 (6%)
#Pancreatic islets	(4[illegible])	(46)	(46)
Hyperplasia, NOS	5 (12%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	2 (4%)		1 (2%)
Hyperplasia, NOS	14 (28%)	27 (54%)	21 (42%)
*Preputial gland	(50)	(50)	(50)
Cystic ducts	2 (4%)	1 (2%)	
Inflammation, NOS	24 (48%)	21 (42%)	23 (46%)
Inflammation, suppurative	5 (10%)	3 (6%)	1 (2%)
Abscess, NOS	2 (6%)		1 (2%)
Inflammation, pyogranulomatous		1 (2%)	
Hyperplasia, epithelial	2 (4%)	4 (8%)	

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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(47)	(45)	(45)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	18 (38%)	10 (22%)	8 (18%)
Hyperplasia, epithelial	4 (9%)	2 (4%)	6 (13%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, NOS	2 (4%)	1 (2%)	4 (8%)
Inflammation, suppurative	14 (28%)	10 (20%)	15 (30%)
Abscess, NOS		1 (2%)	
Fibrosis	1 (2%)		
#Testis	(50)	(49)	(50)
Mineralization	1 (2%)	2 (4%)	3 (6%)
Atrophy, NOS	35 (70%)	38 (78%)	42 (84%)
Hyperplasia, epithelial	1 (2%)		
Hyperplasia, interstitial cell	5 (10%)	6 (12%)	4 (8%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage	2 (4%)	4 (8%)	1 (2%)
Necrosis, focal	2 (4%)	2 (4%)	
Hemosiderosis	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	
Metaplasia, osseous			1 (2%)
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, suppurative		2 (4%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Degeneration, NOS			2 (4%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Mineralization			1 (2%)
*Lacrimal apparatus	(50)	(50)	(50)
Inflammation, NOS		3 (6%)	
Hyperplasia, epithelial		1 (2%)	
Metaplasia, squamous	1 (2%)	3 (6%)	
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative	8 (16%)	7 (14%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Necrosis, fat	1 (2%)	3 (6%)	
Pigmentation, NOS			1 (2%)
Angiectasis			1 (2%)

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TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
Inflammation, active chronic		1 (2%)	
Tail			
Epidermal inclusion cyst	1		
Inflammation, chronic	1	1	
Foot			
Inflammation, chronic		2	
SPECIAL MORPHOLOGY SUMMARY			
None			

# Number of animals with tissue examined microscopically
* Number of animals necropsied

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TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Abscess, NOS		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, NOS	11 (22%)	3 (6%)	12 (24%)
Inflammation, suppurative	8 (16%)	6 (12%)	5 (10%)
Necrosis, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)	3 (6%)	
Metaplasia, squamous	2 (4%)	4 (8%)	2 (4%)
*Larynx	(50)	(50)	(50)
Inflammation, NOS	4 (8%)	1 (2%)	5 (10%)
Inflammation, suppurative	3 (6%)	5 (10%)	3 (6%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
#Trachea	(50)	(49)	(49)
Inflammation, NOS	3 (6%)		2 (4%)
Inflammation, suppurative		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
#Lung/bronchiole	(50)	(49)	(49)
Hyperplasia, epithelial	1 (2%)		
#Lung	(50)	(49)	(49)
Congestion, NOS	1 (2%)	2 (4%)	
Edema, NOS		1 (2%)	1 (2%)
Hemorrhage	1 (2%)	1 (2%)	7 (14%)
Inflammation, NOS	2 (4%)		2 (4%)
Fibrosis	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, alveolar epithelium	5 (10%)	4 (8%)	4 (8%)
Histiocytosis	3 (6%)	6 (12%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(47)	(48)	(46)
Fibrosis	1 (2%)		1 (2%)
#Spleen	(50)	(49)	(49)
Hemorrhage			1 (2%)
Fibrosis			3 (6%)
Necrosis, NOS	1 (2%)		
Hemosiderosis	11 (22%)	3 (6%)	7 (14%)
Hematopoiesis	3 (6%)	2 (4%)	1 (2%)
#Lymph node	(47)	(44)	(45)
Hyperplasia, NOS		1 (2%)	2 (4%)
#Mandibular lymph node	(47)	(44)	(45)
Inflammation, suppurative	1 (2%)		
Hyperplasia, NOS	7 (15%)	9 (20%)	9 (20%)
#Thoracic lymph node	(47)	(44)	(45)
Inflammation, NOS	1 (2%)		
Hemosiderosis		2 (5%)	
Hyperplasia, NOS		1 (2%)	
#Mesenteric lymph node	(47)	(44)	(45)
Hemosiderosis	1 (2%)		
Histiocytosis	1 (2%)		
#Lung	(50)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)	1 (2%)

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TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(50)	(50)	(49)
Leukocytosis, NOS			1 (2%)
Hematopoiesis	1 (2%)	1 (2%)	1 (2%)
#Kidney	(50)	(49)	(50)
Hematopoiesis		1 (2%)	
#Adrenal	(50)	(49)	(47)
Hematopoiesis	1 (2%)	3 (6%)	
#Thymus	(40)	(39)	(35)
Degeneration, cystic	1 (3%)	3 (8%)	
Metaplasia, squamous		1 (3%)	
CIRCULATORY SYSTEM			
*Lacrimal apparatus	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Multiple organs	(50)	(50)	(50)
Perivasculitis			1 (2%)
*Nasal cavity	(50)	(50)	(50)
Thrombosis, NOS	3 (6%)	10 (20%)	7 (14%)
#Heart	(50)	(50)	(49)
Mineralization	1 (2%)		
Thrombosis, NOS	1 (2%)	4 (8%)	2 (4%)
Inflammation, NOS	14 (28%)	19 (38%)	18 (37%)
Fibrosis	27 (54%)	28 (56%)	18 (37%)
*Blood vessel	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
Hypertrophy, NOS	1 (2%)		
#Liver	(50)	(50)	(49)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Oral mucosa	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		
*Tongue	(50)	(50)	(50)
Granuloma, foreign body			1 (2%)
Hyperplasia, epithelial			1 (2%)
*Tooth	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
#Salivary gland	(47)	(48)	(50)
Inflammation, NOS	1 (2%)	3 (6%)	3 (6%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	3 (6%)
Metaplasia, squamous	1 (2%)	6 (13%)	4 (8%)
#Liver	(50)	(50)	(49)
Inflammation, NOS	1 (2%)		1 (2%)
Inflammation, suppurative		2 (4%)	
Inflammation, granulomatous focal	15 (30%)	14 (28%)	16 (33%)
Degeneration, NOS	1 (2%)	3 (6%)	6 (12%)
Degeneration, cystic		1 (2%)	
Degeneration, lipoid	8 (16%)	16 (32%)	8 (16%)
Necrosis, NOS	3 (6%)	6 (12%)	5 (10%)
Pigmentation, NOS	1 (2%)	3 (6%)	1 (2%)
Basophilic cyto change	28 (56%)	25 (50%)	23 (47%)
Eosinophilic cyto change	2 (4%)		
Clear cell change			1 (2%)
Angiectasis		1 (2%)	
Regenerative nodule			1 (2%)
#Liver/periportal	(50)	(50)	(49)
Inflammation, NOS	1 (2%)	1 (2%)	1 (2%)

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TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	6 (12%)	6 (12%)	3 (6%)
#Pancreas	(50)	(47)	(46)
Atrophy, focal	10 (20%)	4 (9%)	6 (13%)
Atrophy, diffuse	3 (6%)		1 (2%)
#Pancreatic acinus	(50)	(47)	(46)
Focal cellular change	1 (2%)	1 (2%)	
*Pharyngeal mucous gland	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Metaplasia, squamous		1 (2%)	
#Glandular stomach	(49)	(49)	(48)
Hemorrhage			1 (2%)
Inflammation, suppurative	1 (2%)		
Erosion	2 (4%)		2 (4%)
#Forestomach	(49)	(49)	(48)
Inflammation, NOS	2 (4%)	2 (4%)	
Ulcer, NOS	3 (6%)	4 (8%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Hyperplasia, epithelial	7 (14%)	5 (10%)	2 (4%)
#Ileum	(49)	(49)	(48)
Parasitism		1 (2%)	
#Colon	(46)	(45)	(42)
Parasitism	8 (17%)	8 (18%)	6 (14%)
*Rectum	(50)	(50)	(50)
Parasitism	1 (2%)		1 (2%)
*Anus	(50)	(50)	(50)
Parasitism			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Cyst, NOS			1 (2%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic focal			1 (2%)
Nephropathy	46 (92%)	46 (94%)	47 (94%)
Nephrosis, NOS		1 (2%)	
Nuclear enlargement		8 (16%)	20 (40%)
Hyperplasia, tubular cell			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)		1 (2%)
#Anterior pituitary	(50)	(48)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Degeneration, cystic	21 (42%)	29 (60%)	30 (60%)
Hyperplasia, NOS	13 (26%)	13 (27%)	11 (22%)
#Adrenal	(50)	(49)	(47)
Fibrosis		1 (2%)	
Degeneration, cystic		1 (2%)	
Degeneration, lipoid	17 (34%)	16 (33%)	14 (30%)
Necrosis, NOS		1 (2%)	2 (4%)
#Adrenal cortex	(50)	(49)	(47)
Cytologic alteration, NOS		1 (2%)	
Hyperplasia, NOS	4 (8%)	6 (12%)	11 (23%)
#Adrenal medulla	(50)	(49)	(47)
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, NOS	7 (14%)	3 (6%)	4 (9%)
#Thyroid	(46)	(48)	(46)
Degeneration, cystic		1 (2%)	
Hyperplasia, C-cell	24 (52%)	12 (25%)	15 (33%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Parathyroid	(27)	(27)	(34)
Hyperplasia, NOS	1 (4%)		
#Pancreatic islets	(50)	(47)	(46)
Hyperplasia, NOS	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
***Mammary gland**	(50)	(50)	(50)
Galactocele			1 (2%)
Fibrosis		1 (2%)	
Hyperplasia, NOS	34 (68%)	39 (78%)	37 (74%)
***Clitoral gland**	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)		1 (2%)
Hyperplasia, focal	3 (6%)	1 (2%)	
#Uterus	(49)	(49)	(50)
Dilatation, NOS	2 (4%)		
Cyst, NOS		1 (2%)	
Hematoma, NOS		1 (2%)	
Inflammation, suppurative			1 (2%)
#Cervix uteri	(49)	(49)	(50)
Hyperplasia, NOS		1 (2%)	3 (6%)
#Uterus/endometrium	(49)	(49)	(50)
Inflammation, suppurative		1 (2%)	
Hyperplasia, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, cystic			1 (2%)
#Ovary	(49)	(49)	(50)
Cyst, NOS	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic			1 (2%)
Degeneration, cystic			1 (2%)
Atrophy, NOS	10 (20%)	7 (14%)	8 (16%)
Hyperplasia, granulosa cell			1 (2%)
Hyperplasia, epithelial	1 (2%)	2 (4%)	3 (6%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
#Brain	(50)	(50)	(50)
Hemorrhage	2 (4%)	3 (6%)	2 (4%)
Necrosis, focal	1 (2%)		1 (2%)
Malacia		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
SPECIAL SENSE ORGANS			
***Eye**	(50)	(50)	(50)
Degeneration, NOS		2 (4%)	1 (2%)
***Eye/crystalline lens**	(50)	(50)	(50)
Mineralization		2 (4%)	1 (2%)
***Lacrimal apparatus**	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	2 (4%)
Inflammation, NOS	1 (2%)	6 (12%)	6 (12%)
Fibrosis		1 (2%)	
Metaplasia, squamous	3 (6%)	3 (6%)	5 (10%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		1 (2%)
Inflammation, suppurative	8 (16%)	6 (12%)	10 (20%)
Hyperplasia, NOS		1 (2%)	

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TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis			1 (2%)
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Inflammation, granulomatous focal		1 (2%)	1 (2%)
Necrosis, fat	1 (2%)	2 (4%)	3 (6%)
Hemosiderosis			1 (2%)
Angiectasis			1 (2%)
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, NOS	1	1	1
Inflammation, granulomatous focal		1	
Degeneration, NOS	1	1	1
Pigmentation, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

# Number of animals with tissue examined microscopically
* Number of animals necropsied

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APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Abscess, NOS	1 (2%)		
Necrosis, focal	1 (2%)		
Atrophy, NOS	1 (2%)	2 (4%)	
Atrophy, focal	2 (4%)		
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
*Subcut tissue	(49)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
Abscess, NOS		2 (4%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	
Inflammation, chronic diffuse	1 (2%)		
Granulation tissue	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Hematoma, NOS		1 (2%)	
Empyema			1 (2%)
Inflammation, chronic focal	30 (61%)	23 (46%)	30 (60%)
*Nasal gland	(49)	(50)	(50)
Cyst, NOS	2 (4%)		
*Nasal septum	(49)	(50)	(50)
Edema, NOS			1 (2%)
*Larynx	(49)	(50)	(50)
Inflammation, chronic focal	1 (2%)	1 (2%)	2 (4%)
*Laryngeal gland	(49)	(50)	(50)
Cyst, NOS	4 (8%)		3 (6%)
#Trachea	(49)	(48)	(50)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial			1 (2%)
Hyperplasia, pseudoepitheliomatous	1 (2%)		
Polyp, NOS			1 (2%)
Metaplasia, squamous			1 (2%)
#Tracheal gland	(49)	(48)	(50)
Cyst, NOS	45 (92%)	26 (54%)	32 (64%)
Necrosis, focal	1 (2%)		
#Bronchial mucous gland	(48)	(49)	(50)
Cyst, NOS	15 (31%)	3 (6%)	6 (12%)
Inflammation, suppurative	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, acute focal	2 (4%)		
Inflammation, chronic focal		1 (2%)	
#Lung/bronchiole	(49)	(49)	(50)
Cytoplasmic aggregate, NOS			1 (2%)

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
RESPIRATORY SYSTEM (Continued)			
#Lung	(49)	(49)	(50)
Mineralization		1 (2%)	
Emphysema, NOS		6 (12%)	1 (2%)
Atelectasis	1 (2%)		
Congestion, acute passive	1 (2%)	8 (16%)	10 (20%)
Edema, NOS			1 (2%)
Hemorrhage		3 (6%)	2 (4%)
Inflammation, interstitial			1 (2%)
Inflammation, acute diffuse		2 (4%)	
Fibrosis, diffuse		1 (2%)	
Perivascular cuffing			1 (2%)
Hyperplasia, alveolar epithelium		2 (4%)	1 (2%)
Bronchiolization	1 (2%)		
Histiocytosis		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Skin	(49)	(50)	(50)
Mastocytosis		1 (2%)	
#Bone marrow	(49)	(49)	(49)
Hemosiderosis			1 (2%)
Myelofibrosis			1 (2%)
#Spleen	(49)	(48)	(50)
Accessory structure		1 (2%)	
Congestion, acute passive	1 (2%)	1 (2%)	
Hematoma, NOS			1 (2%)
Necrosis, focal			1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
Hyperplasia, lymphoid	6 (12%)	2 (4%)	5 (10%)
Hematopoiesis	1 (2%)	4 (8%)	2 (4%)
#Lymph node	(25)	(24)	(27)
Histiocytosis	1 (4%)		
Plasmacytosis			1 (4%)
Hyperplasia, lymphoid	3 (12%)		
#Mandibular lymph node	(25)	(24)	(27)
Hemosiderosis	1 (4%)		
Histiocytosis			3 (11%)
Hyperplasia, lymphoid	2 (8%)		1 (4%)
Mastocytosis	1 (4%)		
#Bronchial lymph node	(25)	(24)	(27)
Necrosis, focal			1 (4%)
Histiocytosis			1 (4%)
Hyperplasia, lymphoid			1 (4%)
#Mediastinal lymph node	(25)	(24)	(27)
Plasmacytosis			1 (4%)
Hematopoiesis		1 (4%)	
#Mesenteric lymph node	(25)	(24)	(27)
Histiocytosis	1 (4%)		
Hyperplasia, lymphoid	3 (12%)		
Hematopoiesis	1 (4%)		1 (4%)
#Lung	(49)	(49)	(50)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	16 (33%)	7 (14%)	11 (22%)
#Liver	(49)	(49)	(50)
Hematopoiesis	3 (6%)	1 (2%)	1 (2%)
#Peyers patch	(49)	(42)	(45)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Kidney	(49)	(49)	(50)
Hematopoiesis	1 (2%)	2 (4%)	
#Thymus	(25)	(18)	(27)
Cyst, NOS	1 (4%)		1 (4%)
CIRCULATORY SYSTEM			
*Peritoneum	(49)	(50)	(50)
Lymphangiectasis	1 (2%)		
Perivasculitis	1 (2%)		
*Larynx	(49)	(50)	(50)
Periarteritis			1 (2%)
#Lung	(49)	(49)	(50)
Thrombosis, NOS			1 (2%)
Perivasculitis	1 (2%)	1 (2%)	1 (2%)
#Heart	(49)	(50)	(50)
Thrombosis, NOS		2 (4%)	1 (2%)
Congestion, acute passive			1 (2%)
Hemorrhage			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, chronic			1 (2%)
Fibrosis		1 (2%)	
Fibrosis, focal		1 (2%)	
Degeneration, NOS			2 (4%)
Necrosis, NOS		1 (2%)	
Necrosis, focal		1 (2%)	
#Endocardium	(49)	(50)	(50)
Inflammation, NOS		1 (2%)	
#Cardiac valve	(49)	(50)	(50)
Degeneration, mucoid	30 (61%)	17 (34%)	25 (50%)
Hemosiderosis	2 (4%)	1 (2%)	1 (2%)
*Aorta	(49)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Coronary artery	(49)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Pulmonary artery	(49)	(50)	(50)
Periarteritis	1 (2%)		
*Pulmonary vein	(49)	(50)	(50)
Thrombosis, NOS		1 (2%)	
Inflammation, chronic		1 (2%)	
#Kidney	(49)	(49)	(50)
Thrombosis, NOS		1 (2%)	
#Testis	(49)	(48)	(49)
Perivasculitis		1 (2%)	
DIGESTIVE SYSTEM			
*Root of tooth	(49)	(50)	(50)
Deformity, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		
Abscess, NOS	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic focal	3 (6%)		
Necrosis, focal	3 (6%)		
*Periodontal tissues	(49)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Salivary gland	(49)	(48)	(48)
Lymphocytic inflammatory infiltrate	12 (24%)	12 (25%)	12 (25%)
Inflammation, chronic focal		1 (2%)	

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)		2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, acute focal		2 (4%)	1 (2%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Fibrosis, focal			1 (2%)
Degeneration, NOS	2 (4%)	4 (8%)	8 (16%)
Degeneration, lipoid		4 (8%)	6 (12%)
Necrosis, NOS	1 (2%)	2 (4%)	5 (10%)
Necrosis, focal		4 (8%)	10 (20%)
Inclusion, nuclear	2 (4%)	5 (10%)	9 (18%)
Cytoplasmic vacuolization			1 (2%)
Basophilic cyto change		2 (4%)	
Focal cellular change		2 (4%)	
Eosinophilic cyto change	1 (2%)	2 (4%)	2 (4%)
Cytoplasmic aggregate, NOS	5 (10%)	2 (4%)	4 (8%)
Hyperplasia, focal			1 (2%)
Angiectasis			1 (2%)
Regeneration, NOS			1 (2%)
#Liver/Kupffer cell	(49)	(49)	(50)
Hyperplasia, focal		1 (2%)	1 (2%)
*Gallbladder	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
#Bile duct	(49)	(49)	(50)
Hyperplasia, focal			1 (2%)
#Pancreas	(47)	(48)	(47)
Lymphocytic inflammatory infiltrate		1 (2%)	
Degeneration, NOS		1 (2%)	
Necrosis, NOS		1 (2%)	
Focal cellular change	1 (2%)		1 (2%)
#Stomach	(48)	(44)	(49)
Erosion			1 (2%)
#Glandular stomach	(48)	(44)	(49)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Dilatation, NOS	1 (2%)		
Cyst, NOS	2 (4%)		2 (4%)
Inflammation, serous			1 (2%)
Inflammation, chronic focal			1 (2%)
Hyperplasia, focal	1 (2%)		2 (4%)
Polyp, NOS		1 (2%)	
Metaplasia, squamous	3 (6%)	1 (2%)	2 (4%)
#Forestomach	(48)	(44)	(49)
Hyperplasia, pseudoepitheliomatous		1 (2%)	
Hyperkeratosis		1 (2%)	1 (2%)
#Intestinal villus	(49)	(42)	(45)
Atrophy, NOS	1 (2%)		
#Duodenum	(49)	(42)	(45)
Inflammation, chronic focal			1 (2%)
#Ileum	(49)	(42)	(45)
Hyperplasia, epithelial	1 (2%)		
*Rectum	(49)	(50)	(50)
Cyst, NOS		2 (4%)	

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Cyst, NOS	3 (6%)	2 (4%)	1 (2%)
Hemorrhage	4 (8%)	2 (4%)	5 (10%)
Lymphocytic inflammatory infiltrate	38 (78%)	27 (55%)	28 (56%)
Inflammation, suppurative			2 (4%)
Nephrosis, NOS	22 (45%)	24 (49%)	28 (56%)
Glomerulosclerosis, NOS		1 (2%)	
Necrosis, NOS	1 (2%)		1 (2%)
Infarct, NOS		1 (2%)	
Hyperplasia, tubular cell	1 (2%)	2 (4%)	4 (8%)
#Kidney/glomerulus	(49)	(49)	(50)
Atrophy, focal			1 (2%)
#Kidney/tubule	(49)	(49)	(50)
Mineralization	1 (2%)		
Cast, NOS	3 (6%)	9 (18%)	15 (30%)
Necrosis, NOS		1 (2%)	
Nuclear enlargement	4 (8%)	17 (35%)	46 (92%)
Eosinophilic cyto change			1 (2%)
Atrophy, focal	1 (2%)		
#Kidney/pelvis	(49)	(49)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Urinary bladder	(48)	(46)	(48)
Ulcer, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
Inflammation, chronic diffuse	1 (2%)		
Granulation tissue			1 (2%)
Hyperplasia, epithelial	1 (2%)		2 (4%)
ENDOCRINE SYSTEM			
#Pituitary	(47)	(41)	(44)
Cyst, NOS	2 (4%)	3 (7%)	2 (5%)
#Adrenal	(49)	(48)	(49)
Accessory structure	1 (2%)		1 (2%)
Necrosis, NOS		2 (4%)	
Atrophy, NOS	1 (2%)		
#Adrenal/capsule	(49)	(48)	(49)
Hyperplasia, NOS	40 (82%)	27 (56%)	29 (59%)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(49)	(48)	(49)
Cyst, NOS	1 (2%)	2 (4%)	3 (6%)
Fibrosis			2 (4%)
Degeneration, NOS	1 (2%)		2 (4%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	3 (6%)	2 (4%)	1 (2%)
#Adrenal medulla	(49)	(48)	(49)
Cyst, NOS	2 (4%)	4 (8%)	1 (2%)
Degeneration, NOS		1 (2%)	
Hyperplasia, focal			3 (6%)
#Thyroid	(47)	(46)	(50)
Cyst, NOS	3 (6%)		1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Hyperplasia, follicular cell	1 (2%)		1 (2%)
#Parathyroid	(20)	(15)	(21)
Cyst, NOS			2 (10%)

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TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Cystic ducts	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal	1 (2%)		
Hyperplasia, NOS	2 (4%)		
*Penis	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, chronic focal			1 (2%)
Necrosis, NOS			1 (2%)
*Prepuce	(49)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)
Abscess, NOS			1 (2%)
Necrosis, NOS			2 (4%)
*Preputial gland	(49)	(50)	(50)
Cyst, NOS	3 (6%)	2 (4%)	4 (8%)
Inflammation, suppurative			1 (2%)
Abscess, NOS	2 (4%)		1 (2%)
Inflammation, chronic diffuse			1 (2%)
#Prostate	(48)	(46)	(44)
Inflammation, suppurative		1 (2%)	
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	3 (6%)
Inflammation, suppurative	1 (2%)	1 (2%)	
Hyperplasia, epithelial			1 (2%)
#Testis	(49)	(48)	(49)
Mineralization	1 (2%)		
Inflammation, acute suppurative			1 (2%)
Atrophy, NOS	1 (2%)	4 (8%)	1 (2%)
Atrophy, focal	1 (2%)	1 (2%)	
Atrophy, diffuse		1 (2%)	
Hyperplasia, interstitial cell		4 (8%)	3 (6%)
#Interstitial cell of Leydig	(49)	(48)	(49)
Inclusion, nuclear		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Fourth ventricle	(49)	(50)	(50)
Dilatation, NOS		1 (2%)	
#Cerebrum	(49)	(50)	(50)
Degeneration, NOS			1 (2%)
#Brain	(49)	(50)	(50)
Gliosis			1 (2%)
Fibrosis, focal		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
#Brain/thalamus	(49)	(50)	(50)
Corpora amylacea	18 (37%)	11 (22%)	25 (50%)
*Olfactory sensory epithelium	(49)	(50)	(50)
Atrophy, focal			1 (2%)
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(49)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	
Inflammation, chronic diffuse			1 (2%)
*Zymbal gland	(49)	(50)	(50)
Inflammation, chronic			1 (2%)

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Skull	(49)	(50)	(50)
Hemorrhage		1 (2%)	
*Sternum	(49)	(50)	(50)
Hematoma, NOS	1 (2%)		
*Skeletal muscle	(49)	(50)	(50)
Fibrosis			1 (2%)
*Cartilage, NOS	(49)	(50)	(50)
Necrosis, focal	2 (4%)	1 (2%)	
*Perichondrium	(49)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic diffuse	1 (2%)		
*Peritoneum	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
Necrosis, fat		1 (2%)	
*Pleura	(49)	(50)	(50)
Inflammation, chronic focal		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Abscess, NOS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
Animal missexed/no necropsy	1		
Auto/necropsy/histo perf		1	

# Number of animals with tissue examined microscopically
* Number of animals necropsied

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Inflammation, acute focal			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	1 (2%)		
Necrosis, NOS		1 (2%)	
Atrophy, NOS	1 (2%)		
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	
Parakeratosis		1 (2%)	
*Subcut tissue	(49)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	28 (57%)	29 (58%)	24 (48%)
Cytoplasmic aggregate, NOS		1 (2%)	
Hyperplasia, focal		1 (2%)	
*Nasal gland	(49)	(50)	(50)
Cyst, NOS		2 (4%)	
*Larynx	(49)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Fibrosis, focal		1 (2%)	
Metaplasia, squamous			1 (2%)
*Laryngeal gland	(49)	(50)	(50)
Cyst, NOS	2 (4%)	4 (8%)	
#Trachea	(48)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
Metaplasia, squamous		1 (2%)	
#Tracheal gland	(48)	(50)	(50)
Cyst, NOS	33 (69%)	16 (32%)	12 (24%)
#Lung/bronchus	(48)	(50)	(50)
Inflammation, chronic focal			1 (2%)
#Bronchial mucous gland	(48)	(50)	(50)
Cyst, NOS	5 (10%)	1 (2%)	2 (4%)
#Lung	(48)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
Emphysema, NOS	2 (4%)	1 (2%)	2 (4%)
Congestion, acute passive	1 (2%)	5 (10%)	6 (12%)
Hemorrhage	3 (6%)	1 (2%)	1 (2%)
Inflammation, interstitial		1 (2%)	
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute diffuse	2 (4%)		
Pneumonia, interstitial chronic			1 (2%)
Inflammation, chronic focal	2 (4%)	3 (6%)	1 (2%)
Thrombophlebitis			1 (2%)
Fibrosis, focal			2 (4%)
Fibrosis, multifocal	1 (2%)		1 (2%)
Fibrosis, diffuse	1 (2%)		
Perivascular cuffing	2 (4%)		
Hyperplasia, alveolar epithelium	1 (2%)		1 (2%)
Histiocytosis		1 (2%)	2 (4%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#Brain	(48)	(49)	(50)
Hematopoiesis		1 (2%)	
*Multiple organs	(49)	(50)	(50)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid			4 (8%)
Hematopoiesis	1 (2%)		2 (4%)
#Bone marrow	(48)	(49)	(48)
Hyperplasia, NOS		1 (2%)	
Myelofibrosis	30 (63%)	30 (61%)	20 (42%)
Hyperplasia, hematopoietic		1 (2%)	
Hypoplasia, hematopoietic			1 (2%)
#Spleen	(49)	(49)	(50)
Necrosis, NOS		1 (2%)	
Hemosiderosis	2 (4%)		
Hyperplasia, lymphoid	3 (6%)	7 (14%)	3 (6%)
Hematopoiesis	6 (12%)	6 (12%)	17 (34%)
#Lymph node	(34)	(31)	(26)
Inflammation, chronic			1 (4%)
#Mandibular lymph node	(34)	(31)	(26)
Hemosiderosis	1 (3%)		
Histiocytosis		1 (3%)	1 (4%)
Hyperplasia, lymphoid	3 (9%)	1 (3%)	
#Bronchial lymph node	(34)	(31)	(26)
Edema, NOS	1 (3%)		
Inflammation, acute diffuse	1 (3%)		
Hemosiderosis	1 (3%)		
Histiocytosis			1 (4%)
Hyperplasia, lymphoid	2 (6%)		
#Mediastinal lymph node	(34)	(31)	(26)
Histiocytosis		1 (3%)	
Plasmacytosis			1 (4%)
#Mesenteric lymph node	(34)	(31)	(26)
Hematopoiesis		1 (3%)	1 (4%)
#Lung	(48)	(50)	(50)
Leukemoid reaction	1 (2%)		
Hyperplasia, lymphoid	21 (44%)	17 (34%)	7 (14%)
#Liver	(48)	(50)	(50)
Hematopoiesis	2 (4%)	3 (6%)	4 (8%)
#Peyers patch	(48)	(45)	(46)
Hyperplasia, lymphoid			1 (2%)
#Kidney	(48)	(49)	(50)
Hematopoiesis	2 (4%)	1 (2%)	4 (8%)
#Adrenal	(47)	(49)	(49)
Hematopoiesis		1 (2%)	
#Adrenal cortex	(47)	(49)	(49)
Hematopoiesis	1 (2%)	1 (2%)	1 (2%)
#Thymus	(35)	(39)	(22)
Edema, NOS			1 (5%)
Inflammation, chronic			1 (5%)
Necrosis, NOS	1 (3%)	1 (3%)	
Atrophy, NOS			1 (5%)

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

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	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Lung	(48)	(50)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
Perivasculitis			2 (4%)
#Heart	(48)	(50)	(50)
Thrombosis, NOS			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		2 (4%)
Fibrosis			1 (2%)
Necrosis, NOS			1 (2%)
#Heart/atrium	(48)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
#Cardiac valve	(48)	(50)	(50)
Degeneration, mucoid	17 (35%)	17 (34%)	7 (14%)
Hemosiderosis	1 (2%)		2. (4%)
#Kidney	(48)	(49)	(50)
Thrombus, organized	1 (2%)		
#Urinary bladder	(46)	(48)	(47)
Periarteritis			1 (2%)
#Ovary	(48)	(49)	(43)
Thrombosis, NOS	2 (4%)		
Periarteritis	1 (2%)		
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
*Periodontal tissues	(49)	(50)	(50)
Abscess, NOS	1 (2%)		
#Salivary gland	(47)	(49)	(49)
Lymphocytic inflammatory infiltrate	6 (13%)	10 (20%)	10 (20%)
Inflammation, chronic focal			2 (4%)
Hemosiderosis		1 (2%)	
#Liver	(48)	(50)	(50)
Mineralization			1 (2%)
Cyst, NOS	1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal		2 (4%)	1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic focal	2 (4%)		3 (6%)
Fibrosis, focal		1 (2%)	
Degeneration, NOS	1 (2%)		12 (24%)
Degeneration, lipid		2 (4%)	1 (2%)
Necrosis, NOS	1 (2%)	3 (6%)	7 (14%)
Necrosis, focal	2 (4%)	2 (4%)	2 (4%)
Inclusion, nuclear		1 (2%)	2 (4%)
Basophilic cyto change			1 (2%)
Focal cellular change		1 (2%)	3 (6%)
Eosinophilic cyto change	1 (2%)	2 (4%)	4 (8%)
Cytoplasmic aggregate, NOS			2 (4%)
Cytoplasmic lipid aggregate			1 (2%)
Angiectasis			2 (4%)
Histiocytosis			1 (2%)
#Hepatic capsule	(48)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Fibrosis, focal	1 (2%)		
*Gallbladder	(49)	(50)	(50)
Dilatation, NOS			1 (2%)
Hypertrophy, NOS			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(47)	(49)	(49)
Cyst, NOS		1 (2%)	
Inflammation, acute diffuse			1 (2%)
Inflammation, chronic focal	1 (2%)		
Inflammation, chronic diffuse	2 (4%)		1 (2%)
Necrosis, focal	1 (2%)		
Focal cellular change			2 (4%)
Atrophy, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, focal			1 (2%)
#Stomach	(48)	(50)	(48)
Inflammation, acute focal		1 (2%)	
#Glandular stomach	(48)	(50)	(48)
Cyst, NOS	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, focal	1 (2%)		
Metaplasia, squamous		2 (4%)	1 (2%)
#Forestomach	(48)	(50)	(48)
Cyst, NOS			2 (4%)
Hyperkeratosis	1 (2%)	5 (10%)	2 (4%)
#Duodenum	(48)	(45)	(46)
Inflammation, chronic focal	1 (2%)		
#Ileum	(48)	(45)	(46)
Amyloidosis		1 (2%)	
*Perirectal tissue	(49)	(50)	(50)
Inflammation, necrotizing	1 (2%)		
*Anus	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)
URINARY SYSTEM			
#Kidney	(48)	(49)	(50)
Hydronephrosis	1 (2%)		
Cyst, NOS			2 (4%)
Congestion, acute passive			2 (4%)
Hemorrhage	1 (2%)	2 (4%)	5 (10%)
Lymphocytic inflammatory infiltrate	29 (60%)	26 (53%)	27 (54%)
Plasma cell infiltrate			1 (2%)
Nephrosis, NOS	5 (10%)	14 (29%)	25 (50%)
Amyloidosis		1 (2%)	
Hyperplasia, tubular cell		1 (2%)	
Metaplasia, osseous			1 (2%)
#Kidney/glomerulus	(48)	(49)	(50)
Atrophy, NOS			1 (2%)
Atrophy, focal	1 (2%)		1 (2%)
#Kidney/tubule	(48)	(49)	(50)
Cast, NOS	4 (8%)	4 (8%)	15 (30%)
Nuclear enlargement		16 (33%)	38 (76%)
Inclusion, nuclear		1 (2%)	
Cytoplasmic crystalline aggregate		1 (2%)	
#Kidney/pelvis	(48)	(49)	(50)
Dilatation, NOS			1 (2%)
#Urinary bladder	(46)	(48)	(47)
Lymphocytic inflammatory infiltrate	4 (9%)	1 (2%)	1 (2%)
Inflammation, chronic focal	5 (11%)	16 (33%)	4 (9%)
Inflammation, chronic diffuse			1 (2%)

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary	(45)	(43)	(42)
Cyst, NOS	1 (2%)	1 (2%)	
Congestion, acute passive		1 (2%)	1 (2%)
Hemorrhage	1 (2%)		
Degeneration, NOS			1 (2%)
Hyperplasia, NOS	1 (2%)	3 (7%)	1 (2%)
Hyperplasia, focal	3 (7%)	7 (16%)	2 (5%)
#Pituitary intermedia	(45)	(43)	(42)
Cyst, NOS	1 (2%)		
#Pituitary cell	(45)	(42)	(42)
Inclusion, nuclear		1 (2%)	
Atypia, NOS		1 (2%)	
#Adrenal	(47)	(49)	(49)
Accessory structure		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	2 (4%)
Necrosis, focal			1 (2%)
Angiectasis		1 (2%)	
#Adrenal/capsule	(47)	(49)	(49)
Hyperplasia, NOS	42 (89%)	41 (84%)	44 (90%)
#Adrenal cortex	(47)	(49)	(49)
Cyst, NOS	2 (4%)	3 (6%)	2 (4%)
Congestion, acute passive		1 (2%)	
Hemorrhage	4 (9%)		1 (2%)
Fibrosis	18 (38%)	26 (53%)	22 (45%)
Degeneration, NOS	19 (40%)	27 (55%)	23 (47%)
Necrosis, NOS	1 (2%)	1 (2%)	
Cytomegaly			1 (2%)
Hyperplasia, focal		1 (2%)	
Vascularization	1 (2%)		
#Adrenal medulla	(47)	(49)	(49)
Cyst, NOS	2 (4%)		2 (4%)
#Periadrenal tissue	(47)	(49)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)
#Thyroid	(48)	(48)	(48)
Cyst, NOS	4 (8%)		
Hyperplasia, follicular cell	1 (2%)	3 (6%)	3 (6%)
#Thyroid follicle	(48)	(48)	(48)
Inflammation, acute focal	1 (2%)		
#Thyroid colloid	(48)	(48)	(48)
Degeneration, NOS	2 (4%)		
#Parathyroid	(18)	(17)	(23)
Cyst, NOS			1 (4%)
Hyperplasia, NOS	1 (6%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	
#Uterus	(43)	(44)	(48)
Hydrometra		2 (5%)	
Hematoma, NOS	1 (2%)	1 (2%)	
Pyometra			3 (6%)
Abscess, NOS			1 (2%)
Necrosis, NOS	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
Metaplasia, squamous	1 (2%)		
#Cervix uteri	(43)	(44)	(48)
Inflammation, chronic			2 (4%)

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Uterus/endometrium	(43)	(44)	(48)
Cyst, NOS	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (5%)		3 (6%)
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, chronic diffuse			1 (2%)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, cystic	31 (72%)	36 (82%)	33 (69%)
Metaplasia, squamous	1 (2%)		
#Uterus/myometrium	(43)	(44)	(48)
Mineralization			1 (2%)
Inflammation, acute			1 (2%)
Granuloma, NOS			1 (2%)
Necrosis, focal			1 (2%)
Cholesterol deposit			1 (2%)
Histiocytosis			1 (2%)
#Fallopian tube	(43)	(44)	(48)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic focal			2 (4%)
Inflammation, chronic diffuse			2 (4%)
#Ovary	(48)	(49)	(43)
Cyst, NOS	12 (25%)	8 (16%)	10 (23%)
Corpus luteum cyst		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, necrotizing	1 (2%)		
Abscess, NOS	1 (2%)		5 (12%)
Inflammation, chronic focal	1 (2%)	2 (4%)	
Inflammation, chronic diffuse	1 (2%)		
Necrosis, focal			1 (2%)
Atrophy, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(49)	(50)
Lymphocytic inflammatory infiltrate			2 (4%)
#Cerebral ventricle	(48)	(49)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
#Ependyma lateral ventricle	(48)	(49)	(50)
Perivascular cuffing		1 (2%)	
#Cerebrum	(48)	(49)	(50)
Cyst, NOS			1 (2%)
Perivascular cuffing		1 (2%)	
Metaplasia, osseous	2 (4%)	1 (2%)	
#Brain	(48)	(49)	(50)
Hemorrhage			1 (2%)
Perivascular cuffing		1 (2%)	
#Brain/thalamus	(48)	(49)	(50)
Corpora amylacea	15 (31%)	10 (20%)	18 (36%)
#Cerebellum	(48)	(49)	(50)
Perivascular cuffing	1 (2%)		
*Olfactory sensory epithelium	(49)	(50)	(50)
Cytoplasmic aggregate, NOS	1 (2%)		

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TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	CONTROL (CHAMBER)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Microphthalmia			1 (2%)
Mineralization	1 (2%)		
*Nasolacrimal duct	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)	2 (4%)
Empyema		1 (2%)	1 (2%)
Inflammation, chronic		3 (6%)	
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
*External ear	(49)	(50)	(50)
Hemorrhage			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skull	(49)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Fibrous osteodystrophy			1 (2%)
*Sternum	(49)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
*Skeletal muscle	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
*Costal cartilage	(49)	(50)	(50)
Necrosis, focal			1 (2%)
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Inflammation, chronic focal	1 (2%)	1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
Inflammation chronic suppurative			1 (2%)
Inflammation, granulomatous focal	1 (2%)		
*Peritoneum	(49)	(50)	(50)
Mineralization	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse			1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic focal	8 (16%)	7 (14%)	7 (14%)
Inflammation, chronic diffuse	5 (10%)	3 (6%)	4 (8%)
Inflammation, chronic suppurative			1 (2%)
Necrosis, focal			1 (2%)
*Pleura	(49)	(50)	(50)
Inflammation, chronic			2 (4%)
Inflammation, chronic focal		1 (2%)	
Granulation tissue			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic focal		2 (4%)	1 (2%)
Inflammation, chronic diffuse			2 (4%)
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1	2	1
Animal missexed/no necropsy	1		

Number of animals with tissue examined microscopically
* Number of animals necropsied

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APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

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TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.1%	5.0%	0.0%
Terminal Rates (c)	1/23 (4%)	1/20 (5%)	0/12 (0%)
Week of First Observation	89	104	
Life Table Tests (d)	P=0.125N	P=0.368N	P=0.231N
Incidental Tumor Tests (d)	P=0.071N	P=0.329N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.0%	5.0%	0.0%
Terminal Rates (c)	1/23 (4%)	1/20 (5%)	0/12 (0%)
Week of First Observation	95	104	
Life Table Tests (d)	P=0.112N	P=0.362N	P=0.200N
Incidental Tumor Tests (d)	P=0.081N	P=0.267N	P=0.130N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	(e) 1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	9.1%	3.0%	23.6%
Terminal Rates (c)	0/23 (0%)	0/20 (0%)	2/12 (17%)
Week of First Observation	98	98	99
Life Table Tests (d)	P=0.260	P=0.358N	P=0.301
Incidental Tumor Tests (d)	P=0.423	P=0.373N	P=0.484
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.309N	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	28/50 (56%)	37/50 (74%)	37/50 (74%)
Adjusted Rates (b)	64.6%	86.1%	90.8%
Terminal Rates (c)	9/23 (39%)	11/20 (55%)	9/12 (75%)
Week of First Observation	66	53	68
Life Table Tests (d)	P=0.004	P=0.046	P=0.004
Incidental Tumor Tests (d)	P=0.097	P=0.023	P=0.104
Cochran-Armitage Trend Test (d)	P=0.034		
Fisher Exact Test (d)		P=0.046	P=0.046
Oral Cavity: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.7%	5.0%	10.8%
Terminal Rates (c)	0/23 (0%)	1/20 (5%)	0/12 (0%)
Week of First Observation	97	104	77
Life Table Tests (d)	P=0.133	P=0.732	P=0.232
Incidental Tumor Tests (d)	P=0.241	P=0.723	P=0.428
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753	P=0.309
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	4/49 (8%)
Adjusted Rates (b)	17.4%	30.6%	30.8%
Terminal Rates (c)	4/23 (17%)	5/20 (25%)	3/12 (25%)
Week of First Observation	104	91	103
Life Table Tests (d)	P=0.192	P=0.177	P=0.267
Incidental Tumor Tests (d)	P=0.285	P=0.195	P=0.330
Cochran-Armitage Trend Test (d)	P=0.553		
Fisher Exact Test (d)		P=0.262	P=0.631

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TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	200 ppm	400 ppm
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	5/49 (10%)
Adjusted Rates (b)	17.4%	30.6%	32.3%
Terminal Rates (c)	4/23 (17%)	5/20 (25%)	3/12 (25%)
Week of First Observation	104	91	83
Life Table Tests (d)	P=0.117	P=0.177	P=0.168
Incidental Tumor Tests (d)	P=0.201	P=0.195	P=0.243
Cochran-Armitage Trend Test (d)	P=0.422		
Fisher Exact Test (d)		P=0.262	P=0.487
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	1/49 (2%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	4.3%	10.8%	12.7%
Terminal Rates (c)	1/23 (4%)	1/20 (5%)	1/12 (8%)
Week of First Observation	104	91	102
Life Table Tests (d)	P=0.242	P=0.259	P=0.316
Incidental Tumor Tests (d)	P=0.350	P=0.296	P=0.376
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.309	P=0.508
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	1/49 (2%)	(f) 3/49 (6%)	4/50 (8%)
Adjusted Rates (b)	4.3%	10.8%	22.4%
Terminal Rates (c)	1/23 (4%)	1/20 (5%)	2/12 (17%)
Week of First Observation	104	91	83
Life Table Tests (d)	P=0.054	P=0.259	P=0.070
Incidental Tumor Tests (d)	P=0.107	P=0.296	P=0.114
Cochran-Armitage Trend Test (d)	P=0.138		
Fisher Exact Test (d)		P=0.309	P=0.187
Pituitary Gland: Adenoma			
Overall Rates (a)	17/47 (36%)	12/47 (26%)	16/48 (33%)
Adjusted Rates (b)	49.2%	50.9%	48.9%
Terminal Rates (c)	7/23 (30%)	9/20 (45%)	1/12 (8%)
Week of First Observation	90	98	73
Life Table Tests (d)	P=0.185	P=0.357N	P=0.238
Incidental Tumor Tests (d)	P=0.484N	P=0.293N	P=0.335N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.186N	P=0.470N
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/47 (6%)	2/47 (4%)	2/48 (4%)
Adjusted Rates (b)	9.6%	7.3%	7.4%
Terminal Rates (c)	0/23 (0%)	1/20 (5%)	0/12 (0%)
Week of First Observation	99	86	85
Life Table Tests (d)	P=0.566N	P=0.575N	P=0.657N
Incidental Tumor Tests (d)	P=0.308N	P=0.514N	P=0.376N
Cochran-Armitage Trend Test (d)	P=0.397N		
Fisher Exact Test (d)		P=0.500N	P=0.490N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	20/47 (43%)	14/47 (30%)	18/48 (38%)
Adjusted Rates (b)	54.2%	56.5%	53.6%
Terminal Rates (c)	7/23 (30%)	10/20 (50%)	1/12 (8%)
Week of First Observation	90	86	73
Life Table Tests (d)	P=0.209	P=0.326N	P=0.259
Incidental Tumor Tests (d)	P=0.352N	P=0.233N	P=0.210N
Cochran-Armitage Trend Test (d)	P=0.346N		
Fisher Exact Test (d)		P=0.142N	P=0.385N

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TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	200 ppm	400 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	22/49 (45%)	21/49 (43%)	23/49 (47%)
Adjusted Rates (b)	64.7%	70.0%	78.0%
Terminal Rates (c)	12/23 (52%)	12/20 (60%)	7/12 (58%)
Week of First Observation	89	82	77
Life Table Tests (d)	P=0.041	P=0.420	P=0.049
Incidental Tumor Tests (d)	P=0.293	P=0.488	P=0.356
Cochran-Armitage Trend Test (d)	P=0.460		
Fisher Exact Test (d)		P=0.500N	P=0.500
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	22/49 (45%)	21/49 (43%)	24/49 (49%)
Adjusted Rates (b)	64.7%	70.0%	82.4%
Terminal Rates (c)	12/23 (52%)	12/20 (60%)	8/12 (67%)
Week of First Observation	89	82	77
Life Table Tests (d)	P=0.025	P=0.420	P=0.030
Incidental Tumor Tests (d)	P=0.212	P=0.488	P=0.259
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.500N	P=0.420
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/47 (6%)	3/48 (6%)	4/46 (9%)
Adjusted Rates (b)	11.5%	12.0%	26.7%
Terminal Rates (c)	2/23 (9%)	1/20 (5%)	2/12 (17%)
Week of First Observation	99	99	102
Life Table Tests (d)	P=0.196	P=0.599	P=0.225
Incidental Tumor Tests (d)	P=0.329	P=0.614	P=0.357
Cochran-Armitage Trend Test (d)	P=0.409		
Fisher Exact Test (d)		P=0.651N	P=0.488
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/47 (9%)	6/48 (13%)	0/46 (0%)
Adjusted Rates (b)	16.4%	24.0%	0.0%
Terminal Rates (c)	3/23 (13%)	3/20 (15%)	0/12 (0%)
Week of First Observation	103	98	
Life Table Tests (d)	P=0.236N	P=0.288	P=0.176N
Incidental Tumor Tests (d)	P=0.139N	P=0.300	P=0.124N
Cochran-Armitage Trend Test (d)	P=0.083N		
Fisher Exact Test (d)		P=0.384	P=0.061N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/47 (15%)	9/48 (19%)	4/46 (9%)
Adjusted Rates (b)	27.0%	33.7%	26.7%
Terminal Rates (c)	5/23 (22%)	4/20 (20%)	2/12 (17%)
Week of First Observation	99	98	102
Life Table Tests (d)	P=0.516	P=0.289	P=0.613
Incidental Tumor Tests (d)	P=0.373N	P=0.300	P=0.464N
Cochran-Armitage Trend Test (d)	P=0.242N		
Fisher Exact Test (d)		P=0.410	P=0.274N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	3/43 (7%)	2/46 (4%)	1/46 (2%)
Adjusted Rates (b)	13.6%	8.2%	3.1%
Terminal Rates (c)	3/22 (14%)	1/20 (5%)	0/12 (0%)
Week of First Observation	104	99	95
Life Table Tests (d)	P=0.375N	P=0.546N	P=0.496N
Incidental Tumor Tests (d)	P=0.297N	P=0.542N	P=0.438N
Cochran-Armitage Trend Test (d)	P=0.200N		
Fisher Exact Test (d)		P=0.468N	P=0.283N

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TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	200 ppm	400 ppm
Preputial Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	4.3%	11.2%	19.8%
Terminal Rates (c)	1/23 (4%)	1/20 (5%)	2/12 (17%)
Week of First Observation	104	87	99
Life Table Tests (d)	P=0.107	P=0.255	P=0.137
Incidental Tumor Tests (d)	P=0.170	P=0.285	P=0.164
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Preputial Gland: Carcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8.0%	10.0%	15.0%
Terminal Rates (c)	1/23 (4%)	2/20 (10%)	1/12 (8%)
Week of First Observation	103	104	86
Life Table Tests (d)	P=0.205	P=0.637	P=0.285
Incidental Tumor Tests (d)	P=0.318	P=0.688	P=0.467
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	12.2%	20.6%	33.0%
Terminal Rates (c)	2/23 (9%)	3/20 (15%)	3/12 (25%)
Week of First Observation	103	87	86
Life Table Tests (d)	P=0.047	P=0.277	P=0.063
Incidental Tumor Tests (d)	P=0.112	P=0.299	P=0.139
Cochran-Armitage Trend Test (d)	P=0.195		
Fisher Exact Test (d)		P=0.357	P=0.243
Testis: Interstitial Cell Tumor			
Overall Rates (a)	35/50 (70%)	39/49 (80%)	41/50 (82%)
Adjusted Rates (b)	91.4%	97.5%	100.0%
Terminal Rates (c)	20/23 (87%)	19/20 (95%)	12/12 (100%)
Week of First Observation	69	82	68
Life Table Tests (d)	P<0.001	P=0.093	P=0.001
Incidental Tumor Tests (d)	P=0.012	P=0.047	P=0.024
Cochran-Armitage Trend Test (d)	P=0.095		
Fisher Exact Test (d)		P=0.193	P=0.121
Brain: Glioma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	4.8%	0.0%	17.3%
Terminal Rates (c)	1/23 (4%)	0/20 (0%)	0/12 (0%)
Week of First Observation	104		88
Life Table Tests (d)	P=0.039	P=0.528N	P=0.083
Incidental Tumor Tests (d)	P=0.103	P=0.528N	P=0.207
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
All Sites: Mesothelioma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	6.3%	4.8%	15.3%
Terminal Rates (c)	1/23 (4%)	0/20 (0%)	1/12 (8%)
Week of First Observation	69	103	91
Life Table Tests (d)	P=0.254	P=0.548N	P=0.342
Incidental Tumor Tests (d)	P=0.422	P=0.461N	P=0.509
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500

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TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A fibrosarcoma was also present in this animal.
(f) A nephroblastoma and a lipoma were also observed in this group.

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TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	200 ppm	400 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	18/50 (36%)	30/50 (60%)	29/50 (58%)
Adjusted Rates (b)	53.8%	71.4%	66.3%
Terminal Rates (c)	9/23 (39%)	10/21 (48%)	10/24 (42%)
Week of First Observation	84	60	76
Life Table Tests (d)	P=0.053	P=0.023	P=0.053
Incidental Tumor Tests (d)	P=0.012	P=0.013	P=0.014
Cochran-Armitage Trend Test (d)	P=0.018		
Fisher Exact Test (d)		P=0.014	P=0.022
Pituitary Gland: Adenoma			
Overall Rates (a)	19/50 (38%)	21/48 (44%)	20/50 (40%)
Adjusted Rates (b)	55.6%	63.7%	60.9%
Terminal Rates (c)	9/23 (39%)	10/20 (50%)	12/24 (50%)
Week of First Observation	59	60	76
Life Table Tests (d)	P=0.471	P=0.304	P=0.514
Incidental Tumor Tests (d)	P=0.479	P=0.245	P=0.513
Cochran-Armitage Trend Test (d)	P=0.459		
Fisher Exact Test (d)		P=0.354	P=0.500
Pituitary Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	2/48 (4%)	3/50 (6%)
Adjusted Rates (b)	13.9%	5.6%	10.5%
Terminal Rates (c)	2/23 (9%)	0/20 (0%)	2/24 (8%)
Week of First Observation	87	90	85
Life Table Tests (d)	P=0.422N	P=0.276N	P=0.494N
Incidental Tumor Tests (d)	P=0.458N	P=0.357N	P=0.533N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.359N	P=0.500N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	23/50 (46%)	23/48 (48%)	23/50 (46%)
Adjusted Rates (b)	64.1%	66.8%	68.2%
Terminal Rates (c)	11/23 (48%)	10/20 (50%)	14/24 (58%)
Week of First Observation	59	60	76
Life Table Tests (d)	P=0.523N	P=0.426	P=0.554N
Incidental Tumor Tests (d)	P=0.539	P=0.493	P=0.575
Cochran-Armitage Trend Test (d)	P=0.540		
Fisher Exact Test (d)		P=0.505	P=0.579
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	0/49 (0%)	3/47 (6%)
Adjusted Rates (b)	4.3%	0.0%	11.4%
Terminal Rates (c)	1/23 (4%)	0/21 (0%)	2/23 (9%)
Week of First Observation	104		95
Life Table Tests (d)	P=0.176	P=0.518N	P=0.300
Incidental Tumor Tests (d)	P=0.171	P=0.518N	P=0.292
Cochran-Armitage Trend Test (d)	P=0.162		
Fisher Exact Test (d)		P=0.505N	P=0.285
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/46 (7%)	1/48 (2%)	3/46 (7%)
Adjusted Rates (b)	9.3%	4.8%	9.8%
Terminal Rates (c)	0/22 (0%)	1/21 (5%)	1/23 (4%)
Week of First Observation	89	104	89
Life Table Tests (d)	P=0.587	P=0.331N	P=0.650
Incidental Tumor Tests (d)	P=0.511	P=0.311N	P=0.547
Cochran-Armitage Trend Test (d)	P=0.595		
Fisher Exact Test (d)		P=0.292N	P=0.662

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TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	200 ppm	400 ppm
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	1/46 (2%)	4/48 (8%)	1/46 (2%)
Adjusted Rates (b)	3.8%	15.1%	4.3%
Terminal Rates (c)	0/22 (0%)	2/21 (10%)	1/23 (4%)
Week of First Observation	103	96	104
Life Table Tests (d)	P=0.596N	P=0.168	P=0.760N
Incidental Tumor Tests (d)	P=0.560	P=0.173	P=0.737
Cochran-Armitage Trend Test (d)	P=0.602		
Fisher Exact Test (d)		P=0.194	P=0.753
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/46 (9%)	5/48 (10%)	4/46 (9%)
Adjusted Rates (b)	12.9%	19.6%	13.9%
Terminal Rates (c)	0/22 (0%)	3/21 (14%)	2/23 (9%)
Week of First Observation	89	96	89
Life Table Tests (d)	P=0.567	P=0.464	P=0.632
Incidental Tumor Tests (d)	P=0.479	P=0.490	P=0.525
Cochran-Armitage Trend Test (d)	P=0.571		
Fisher Exact Test (d)		P=0.527	P=0.643
Mammary Gland: Fibroadenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	21.1%	10.3%	18.5%
Terminal Rates (c)	3/23 (13%)	1/21 (5%)	2/24 (8%)
Week of First Observation	87	96	77
Life Table Tests (d)	P=0.457N	P=0.194N	P=0.517N
Incidental Tumor Tests (d)	P=0.465N	P=0.158N	P=0.532N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test (d)		P=0.159N	P=0.500N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	21.1%	10.3%	20.8%
Terminal Rates (c)	3/23 (13%)	1/21 (5%)	2/24 (8%)
Week of First Observation	87	96	77
Life Table Tests (d)	P=0.541	P=0.194N	P=0.590
Incidental Tumor Tests (d)	P=0.528	P=0.158N	P=0.575
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Test (d)		P=0.159N	P=0.613
Mammary Gland: Adenoma, Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	25.1%	14.4%	20.8%
Terminal Rates (c)	4/23 (17%)	1/21 (5%)	2/24 (8%)
Week of First Observation	87	73	77
Life Table Tests (d)	P=0.459N	P=0.318N	P=0.515N
Incidental Tumor Tests (d)	P=0.453N	P=0.262N	P=0.536N
Cochran-Armitage Trend Test (d)	P=0.442N		
Fisher Exact Test (d)		P=0.277N	P=0.500N
Clitoral Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	11.3%	4.8%	8.3%
Terminal Rates (c)	2/23 (9%)	1/21 (5%)	2/24 (8%)
Week of First Observation	98	104	104
Life Table Tests (d)	P=0.392N	P=0.335N	P=0.493N
Incidental Tumor Tests (d)	P=0.395N	P=0.330N	P=0.498N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309N	P=0.500N

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TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	200 ppm	400 ppm
Clitoral Gland: Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	6.4%	9.3%	8.3%
Terminal Rates (c)	1/23 (4%)	1/21 (5%)	2/24 (8%)
Week of First Observation	84	85	104
Life Table Tests (d)	P=0.588	P=0.475	P=0.691N
Incidental Tumor Tests (d)	P=0.567	P=0.510	P=0.686
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.500	P=0.691
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	17.4%	13.8%	16.7%
Terminal Rates (c)	3/23 (13%)	2/21 (10%)	4/24 (17%)
Week of First Observation	84	85	104
Life Table Tests (d)	P=0.427N	P=0.541N	P=0.492N
Incidental Tumor Tests (d)	P=0.447N	P=0.512N	P=0.505N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	5/49 (10%)	7/49 (14%)	7/50 (14%)
Adjusted Rates (b)	16.6%	23.1%	23.5%
Terminal Rates (c)	2/23 (9%)	2/21 (10%)	4/24 (17%)
Week of First Observation	96	85	88
Life Table Tests (d)	P=0.230	P=0.345	P=0.382
Incidental Tumor Tests (d)	P=0.272	P=0.343	P=0.334
Cochran-Armitage Trend Test (d)	P=0.340		
Fisher Exact Test (d)		P=0.380	P=0.394
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	5/49 (10%)	9/49 (18%)	8/50 (16%)
Adjusted Rates (b)	16.6%	29.1%	27.3%
Terminal Rates (c)	2/23 (9%)	3/21 (14%)	5/24 (21%)
Week of First Observation	96	85	88
Life Table Tests (d)	P=0.250	P=0.177	P=0.283
Incidental Tumor Tests (d)	P=0.194	P=0.170	P=0.241
Cochran-Armitage Trend Test (d)	P=0.253		
Fisher Exact Test (d)		P=0.194	P=0.290

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

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TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	100 ppm	200 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	5/49 (10%)	1/50 (2%)
Adjusted Rates (b)	6.5%	18.3%	3.1%
Terminal Rates (c)	3/46 (7%)	4/25 (16%)	1/32 (3%)
Week of First Observation	104	89	104
Life Table Tests (d)	P=0.446N	P=0.110	P=0.442N
Incidental Tumor Tests (d)	P=0.378N	P=0.196	P=0.442N
Cochran-Armitage Trend Test (d)	P=0.256N		
Fisher Exact Test (d)		P=0.357	P=0.301N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	4/49 (8%)	1/49 (2%)	4/50 (8%)
Adjusted Rates (b)	8.7%	4.0%	12.0%
Terminal Rates (c)	4/46 (9%)	1/25 (4%)	3/32 (9%)
Week of First Observation	104	104	103
Life Table Tests (d)	P=0.390	P=0.401N	P=0.440
Incidental Tumor Tests (d)	P=0.441	P=0.401N	P=0.522
Cochran-Armitage Trend Test (d)	P=0.573N		
Fisher Exact Test (d)		P=0.181N	P=0.631N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	6/49 (12%)	5/50 (10%)
Adjusted Rates (b)	13.0%	22.2%	15.1%
Terminal Rates (c)	6/46 (13%)	5/25 (20%)	4/32 (13%)
Week of First Observation	104	89	103
Life Table Tests (d)	P=0.414	P=0.220	P=0.507
Incidental Tumor Tests (d)	P=0.502	P=0.335	P=0.578
Cochran-Armitage Trend Test (d)	P=0.423N		
Fisher Exact Test (d)		P=0.629	P=0.486N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/49 (6%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	6.5%	20.3%	9.4%
Terminal Rates (c)	3/46 (7%)	2/25 (8%)	3/32 (9%)
Week of First Observation	104	55	104
Life Table Tests (d)	P=0.378	P=0.043	P=0.487
Incidental Tumor Tests (d)	P=0.496N	P=0.406	P=0.487
Cochran-Armitage Trend Test (d)	P=0.558N		
Fisher Exact Test (d)		P=0.167	P=0.652N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	6.5%	7.7%	6.2%
Terminal Rates (c)	3/46 (7%)	1/25 (4%)	2/32 (6%)
Week of First Observation	104	102	104
Life Table Tests (d)	P=0.576N	P=0.601	P=0.662N
Incidental Tumor Tests (d)	P=0.517N	P=0.638N	P=0.662N
Cochran-Armitage Trend Test (d)	P=0.398N		
Fisher Exact Test (d)		P=0.491N	P=0.491N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	11/49 (22%)	8/49 (16%)	18/50 (36%)
Adjusted Rates (b)	23.9%	29.9%	52.4%
Terminal Rates (c)	11/46 (24%)	7/25 (28%)	16/32 (50%)
Week of First Observation	104	89	73
Life Table Tests (d)	P=0.005	P=0.345	P=0.006
Incidental Tumor Tests (d,e)	P=0.009	P=0.463	P=0.013
Cochran-Armitage Trend Test (d)	P=0.073		
Fisher Exact Test (d)		P=0.305N	P=0.104

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TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

	Control	100 ppm	200 ppm
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	7/49 (14%)	25/49 (51%)	26/50 (52%)
Adjusted Rates (b)	14.9%	58.3%	58.3%
Terminal Rates (c)	6/46 (13%)	8/25 (32%)	14/32 (44%)
Week of First Observation	98	63	60
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d,f)	P=0.002	P=0.016	P=0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/49 (33%)	31/49 (63%)	40/50 (80%)
Adjusted Rates (b)	34.0%	73.0%	86.8%
Terminal Rates (c)	15/46 (33%)	14/25 (56%)	26/32 (81%)
Week of First Observation	98	63	60
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d,g)	P<0.001	P=0.017	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.002	P<0.001

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test, which regards these lesions as nonfatal, lacks sensitivity because the unusually good survival in the control group creates unsatisfactory comparisons in the early time intervals. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(e) P values determined with intervals of weeks 0-52 and 53-103 and week 104: 0.009, 0.438, 0.014

(f) P values determined with intervals of weeks 0-52 and 53-103 and week 104: 0.003, 0.021, 0.001

(g) P values determined with intervals of weeks 0-52 and 53-103 and week 104: <0.001, 0.020, <0.001

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TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE

	Control	100 ppm	200 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/48 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.1%	6.2%	2.4%
Terminal Rates (c)	4/36 (11%)	1/31 (3%)	0/19 (0%)
Week of First Observation	104	102	85
Life Table Tests (d)	P=0.252N	P=0.403N	P=0.362N
Incidental Tumor Tests (d)	P=0.112N	P=0.396N	P=0.220N
Cochran-Armitage Trend Test (d)	P=0.108N		
Fisher Exact Test (d)		P=0.319N	P=0.168N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/48 (13%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	16.7%	9.3%	9.5%
Terminal Rates (c)	6/36 (17%)	2/31 (6%)	1/19 (5%)
Week of First Observation	104	102	67
Life Table Tests (d)	P=0.411N	P=0.317N	P=0.524N
Incidental Tumor Tests (d)	P=0.216N	P=0.211N	P=0.339N
Cochran-Armitage Trend Test (d)	P=0.162N		
Fisher Exact Test (d)		P=0.223N	P=0.223N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	8/49 (16%)	13/50 (26%)	8/50 (16%)
Adjusted Rates (b)	19.4%	35.2%	29.4%
Terminal Rates (c)	4/36 (11%)	8/31 (26%)	4/19 (21%)
Week of First Observation	93	34	54
Life Table Tests (d)	P=0.193	P=0.104	P=0.268
Incidental Tumor Tests (d)	P=0.418N	P=0.159	P=0.485N
Cochran-Armitage Trend Test (d)	P=0.531N		
Fisher Exact Test (d)		P=0.176	P=0.590N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.8%	9.7%	0.0%
Terminal Rates (c)	1/36 (3%)	3/31 (10%)	0/19 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.576N	P=0.253	P=0.627N
Incidental Tumor Tests (d)	P=0.576N	P=0.253	P=0.627N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.316	P=0.495N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.8%	9.7%	5.3%
Terminal Rates (c)	1/36 (3%)	3/31 (10%)	1/19 (5%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.386	P=0.253	P=0.613
Incidental Tumor Tests (d)	P=0.386	P=0.253	P=0.613
Cochran-Armitage Trend Test (d)	P=0.603N		
Fisher Exact Test (d)		P=0.316	P=0.748N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/48 (6%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	7.5%	18.7%	6.1%
Terminal Rates (c)	1/36 (3%)	5/31 (16%)	0/19 (0%)
Week of First Observation	96	102	78
Life Table Tests (d)	P=0.479	P=0.182	P=0.641N
Incidental Tumor Tests (d)	P=0.325N	P=0.193	P=0.213N
Cochran-Armitage Trend Test (d)	P=0.401N		
Fisher Exact Test (d)		P=0.264	P=0.481N

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TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TETRACHLOROETHYLENE (Continued)

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	Control	100 ppm	200 ppm
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/48 (2%)	13/50 (26%)	36/50 (72%)
Adjusted Rates (b)	2.8%	35.5%	91.7%
Terminal Rates (c)	1/36 (3%)	8/31 (26%)	16/19 (84%)
Week of First Observation	104	76	67
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/48 (8%)	17/50 (34%)	38/50 (76%)
Adjusted Rates (b)	10.1%	46.7%	92.2%
Terminal Rates (c)	2/36 (6%)	12/31 (39%)	16/19 (84%)
Week of First Observation	96	76	67
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.002	P<0.001
Pituitary Gland: Carcinoma			
Overall Rates (a)	5/45 (11%)	3/43 (7%)	3/42 (7%)
Adjusted Rates (b)	14.7%	9.7%	15.4%
Terminal Rates (c)	5/34 (15%)	3/31 (10%)	2/17 (12%)
Week of First Observation	104	104	102
Life Table Tests (d)	P=0.549	P=0.406N	P=0.573
Incidental Tumor Tests (d)	P=0.544N	P=0.406N	P=0.645N
Cochran-Armitage Trend Test (d)	P=0.316N		
Fisher Exact Test (d)		P=0.383N	P=0.396N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	7/45 (16%)	3/43 (7%)	5/42 (12%)
Adjusted Rates (b)	19.7%	9.7%	20.5%
Terminal Rates (c)	6/34 (18%)	3/31 (10%)	2/17 (12%)
Week of First Observation	97	104	88
Life Table Tests (d)	P=0.480	P=0.200N	P=0.473
Incidental Tumor Tests (d)	P=0.387N	P=0.193N	P=0.462N
Cochran-Armitage Trend Test (d)	P=0.340N		
Fisher Exact Test (d)		P=0.176N	P=0.429N
Harderian Gland: Adenoma or Carcinoma (e)			
Overall Rates (a)	1/49 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.4%	3.2%	14.3%
Terminal Rates (c)	0/36 (0%)	1/31 (3%)	2/19 (11%)
Week of First Observation	97	104	102
Life Table Tests (d)	P=0.093	P=0.726	P=0.155
Incidental Tumor Tests (d)	P=0.202	P=0.726	P=0.325
Cochran-Armitage Trend Test (d)	P=0.207		
Fisher Exact Test (d)		P=0.747N	P=0.316

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(e) Includes adenoma, NOS, papillary adenoma, and papillary carcinoma

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APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT

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TABLE F1. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Leukemia in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	20/50
Propylene	16/50
TOTAL	36/100 (36.0%)
Overall Historical Incidence	
TOTAL	458/1,727 (26.5%)
SD (b)	8.83%
Range (c)	
High	23/50
Low	5/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	3/48	0/48	3/48
Propylene	3/50	2/50	5/50
TOTAL	6/98 (6.1%)	2/98 (2.0%)	8/98 (8.2%)
Overall Historical Incidence			
TOTAL	338/1,702 (19.9%)	20/1,702 (1.2%)	358/1,702 (21.0%)
SD (b)	9.87%	1.49%	9.63%
Range (c)			
High	20/49	3/48	21/49
Low	2/50	0/50	3/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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TABLE F3. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Interstitial Cell Tumors in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	29/49
Propylene	37/50
TOTAL	66/99 (66.7%)
Overall Historical Incidence	
TOTAL	(b) 1,511/1,703 (88.7%)
SD (c)	7.79%
Range (d)	
High	49/50
Low	34/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Total includes one interstitial cell tumor, malignant.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

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TABLE F4. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	0/50
Propylene	0/50
TOTAL	0/100 (0.0%)
Overall Historical Incidence	
TOTAL	(b) 4/1,720 (0.2%)
SD (c)	0.65%
Range (d)	
High	1/50
Low	0/90

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes one adenoma, NOS. No malignant tubular cell tumors have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls Adenoma	Carcinoma or Adenocarcinoma	Adenoma, Carcinoma, or Adenocarcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Propylene	0/50	0/50	0/50
TOTAL	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)
Overall Historical Incidence			
TOTAL	(b) 48/1,727 (2.8%)	(c) 57/1,727 (3.3%)	(b,c) 105/1,727 (6.1%)
SD (d)	3.75%	2.98%	4.62%
Range (e)			
High	8/50	5/50	8/50
Low	0/90	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes 1 cystadenoma, 1 papillary adenoma, and 46 adenomas, NOS
(c) Includes 2 squamous cell carcinomas, 7 adenocarcinomas, NOS, 2 sebaceous adenocarcinomas, and 46 carcinomas, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

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TABLE F6. HISTORICAL INCIDENCE OF BRAIN TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	47	1	Glioma, NOS
Propylene	50	1	Astrocytoma
TOTAL	97	2 (2.1%)	
Overall Historical Incidence			
	1,721	4	Glioma, NOS
		7	Astrocytoma
		2	Oligodendroglioma
		1	Granular cell tumor, benign
		2	Granular cell tumor, NOS
		1	Granular cell tumor, malignant
		1	Medulloblastoma
		1	Meningioma
TOTAL		(b) 13 (0.8%)	

(a) Data as of August 3, 1984. Totals and range are for neuroglial cell tumors (glioma, astrocytoma, and oligodendroglioma). Other tumors are reported for comparison purposes.
(b) The greatest incidence observed in any control group is 3/50.

TABLE F7. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Leukemia in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	14/50
Propylene	13/49
TOTAL	27/99 (27.3%)
Overall Historical Incidence	
TOTAL	307/1,772 (17.3%)
SD (b)	6.00%
Range (c)	
High	19/50
Low	3/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	8/50	6/50	14/50
Propylene	5/50	9/50	14/50
TOTAL	13/100 (13.0%)	15/100 (15.0%)	28/100 (28.0%)
Overall Historical Incidence			
TOTAL	179/1,784 (10.0%)	377/1,784 (21.1%)	540/1,784 (30.3%)
SD (b)	7.36%	6.54%	8.04%
Range (c)			
High	(d) 22/50	16/50	(e) 29/50
Low	0/49	4/50	7/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest incidence: 9/50
(e) Second highest incidence: 20/50

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TABLE F9. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/50	2/50	3/50
Propylene	0/50	2/50	2/50
TOTAL	1/100 (1.0%)	4/100 (4.0%)	5/100 (5.0%)
Overall Historical Incidence			
TOTAL	68/1,781 (3.8%)	(b) 82/1,781 (4.6%)	147/1,781 (8.3%)
SD (c)	4.14%	3.08%	4.76%
Range (d)			
High	9/49	7/48	10/49
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks

(b) One hepatoblastoma also was observed.

(c) Standard deviation

(d) Range and SD are presented for groups of 35 or more animals.

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APPENDIX G

GENETIC TOXICOLOGY OF TETRACHLOROETHYLENE

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TABLE G1. MUTAGENICITY OF TETRACHLOROETHYLENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a, b) −S9	Revertants/plate (a, b) +S9 (rat)	Revertants/plate (a, b) +S9 (hamster)
TA100	0	83 ± 3.7	143 ± 6.7	97 ± 16.2
	3.3	82 ± 5.2	167 ± 17.9	105 ± 1.3
	10	87 ± 2.0	168 ± 6.1	92 ± 6.8
	33	79 ± 1.7	156 ± 10.5	102 ± 14.5
	100	75 ± 5.6	159 ± 3.9	118 ± 8.1
	333	70 ± 7.0	93 ± 4.1	77 ± 2.6
TA1535	0	22 ± 2.3	18 ± 1.5	9 ± 0.6
	3.3	15 ± 0.7	15 ± 2.0	9 ± 0.6
	10	17 ± 2.7	16 ± 1.5	8 ± 0.9
	33	19 ± 2.6	14 ± 2.3	10 ± 0.7
	100	23 ± 3.5	17 ± 1.2	11 ± 3.2
	333	Toxic	12 ± 2.1	8 ± 1.8
TA1537	0	7 ± 0.9	7 ± 0.2	10 ± 2.6
	3.3	7 ± 1.2	7 ± 0.6	7 ± 0.3
	10	8 ± 3.0	11 ± 2.2	10 ± 0.7
	33	9 ± 0.3	7 ± 1.5	14 ± 1.2
	100	7 ± 2.6	8 ± 0.9	11 ± 0.6
	333	Toxic	7 ± 0.3	6 ± 0.0
TA98	0	17 ± 0.9	36 ± 3.2	22 ± 3.5
	3.3	15 ± 2.6	39 ± 4.5	24 ± 2.6
	10	20 ± 2.8	31 ± 1.3	27 ± 4.6
	33	16 ± 2.2	36 ± 7.3	29 ± 3.2
	100	13 ± 4.2	40 ± 2.7	34 ± 2.3
	333	10 ± 0.5	31 ± 2.1	26 ± 1.7

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (dimethyl sulfoxide) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

(b) Mean ± standard error

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TABLE G2. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY (CHO) CELLS BY TETRACHLOROETHYLENE

− S9 (a) Dose (µg/ml)	SCE/Cell	+ S9 (b) Dose (µg/ml)	SCE/Cell
DMSO (10 µl)	9.1	DMSO (10 µl)	9.3
Tetrachloroethylene		Tetrachloroethylene	
16.4	8.5	80.36	9.2
54.5	8.9	109.90	8.6
164.0	8.5	124.60	8.7
Triethylenemelamine (0.015)	50.6	Cyclophosphamide (1.5)	29.0

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation continued for 24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, treated for 3 minutes with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978).

(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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TABLE G3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY (CHO) CELLS BY TETRACHLOROETHYLENE

− S9 (a) Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	+ S9 (b) Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO (10 µl)	3 (1.8)	DMSO (10 µl)	4 (4)
Tetrachloroethylene		Tetrachloroethylene	
17.0	5 (5.0)	17.0	1 (1)
34.1	2 (2.0)	34.1	1 (1)
68.1	1 (3.4)	68.1	2 (1)
136.3	5 (5.0)		
Triethylenemelamine (0.5)	23 (18.0)	Cyclophosphamide (25)	24 (21)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE G2. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY (CHO) CELLS BY TETRACHLOROETHYLENE

−S9 (a)		+S9 (b)	
Dose (µg/ml)	SCE/Cell	Dose (µg/ml)	SCE/Cell
DMSO (10 µl)	9.1	DMSO (10 µl)	9.3
Tetrachloroethylene		Tetrachloroethylene	
16.4	8.5	80.36	9.2
54.5	8.9	109.90	8.6
164.0	8.5	124.60	8.7
Triethylenemelamine (0.015)	50.6	Cyclophosphamide (1.5)	29.0

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation continued for 24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, treated for 3 minutes with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978).

(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE G3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY (CHO) CELLS BY TETRACHLOROETHYLENE

−S9 (a)		+S9 (b)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO (10 µl)	3 (1.0)	DMSO (10 µl)	4 (4)
Tetrachloroethylene		Tetrachloroethylene	
17.0	5 (5.0)	17.0	1 (1)
34.1	2 (2.0)	34.1	1 (1)
68.1	1 (3.4)	68.1	2 (1)
136.3	5 (5.0)		
Triethylenemelamine (0.5)	23 (18.0)	Cyclophosphamide (25)	24 (21)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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TABLE G4. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY TETROCHLOROETHYLENE

Route of Exposure	Dose (ppm)	No. of Lethals/No. of X Chromosomes Tested (a)				
		Mating 1	Mating 2	Mating 3	Total	(percent)
Feeding	0	2/2,202	2/2,177	5/2,206	9/6,585	(0.14)
	4,000	3/2,166	3/2,145	1/2,238	7/6,549	(0.11)
Injection	0	3/3,295	3/2,868	4/2,482	10/8,654	(0.12)
	1,000	4/3,233	2/2,879	1/2,374	7/8,485	(0.08)

(a) The sex-linked recessive lethal assay was performed essentially as described by Abrahamson and Lewis (1971). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the test chemical dissolved in 5% sucrose. Exposure by injection was done by injecting 72-hour-old adult males at the base of the halteres with enough of the test chemical dissolved in 0.7% sodium chloride to distend the abdomen (approximately 0.3 µl). Injected flies were allowed to recover for 24 hours before being mated. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days, after which the parents were discarded. F_1 heterozygous females were crossed to their sibs and placed in individual vials. F_1 daughters from the same parental males were kept together to identify clusters; none was found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Z values were −0.4893 for feeding and −0.6897 for injection. Analysis of the data according to Margolin et al. (1983) showed that the test chemical did not cause a significant increase in sex-linked recessive lethal mutations at the 5% level of significance.

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TABLE G5. MUTAGENICITY OF TETRACHLOROETHYLENE IN L5178Y/TK+/- MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Compound (Dose)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO (1%)	75	86.5	100	29
	133	104.5	100	42
	106	107.2	100	33
	98	88.2	100	37
3-Methylcholanthrene				
(2.5 µg/ml)	687	108.3	69.8	211
	617	94.3	81.6	218
	614	108.5	87.1	189
Tetrachloroethylene (nl/ml)				
6.25	90	79.5	98.8	38
	67	81.0	85.7	28
	92	80.0	86.2	38
12.50	68	62.3	50.4	36
	44	54.3	55.8	27
	103	80.2	67.4	43
25.00	71	61.8	64.1	38
	100	82.0	61.7	41
	112	93.7	72.5	40
50.00	78	103.2	77.2	25
	86	81.7	40.7	35
100.00	128	78.0	8.4	55
	122	97.3	39.2	42

(a) Experiments were performed twice, and all doses were tested in duplicate or triplicate. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the livers of Aroclor 1254-induced male F/344 rats.

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TABLE G6. MUTAGENICITY OF TETRACHLOROETHYLENE IN L5178Y/TK+/- MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO (1%)	61	93.0	100	22
	78	100.8	100	26
	74	101.5	100	24
Ethyl methanesulfonate (250 µg/ml)	976	79.8	76.5	408
	947	96.2	92.1	328
Tetrachloroethylene (nl/ml)				
12.5	50	57.8	70.7	29
	69	70.8	72.1	32
	80	72.3	62.0	37
25.0	76	79.0	57.5	32
	94	103.8	64.5	30
	91	95.5	64.4	32
50.0	54	70.8	45.2	25
	76	96.5	64.1	26
	71	63.3	35.8	37
75.0	64	71.0	38.9	30
	50	53.7	30.4	31
	82	74.8	30.9	37
150.0	66	84.2	37.9	26
	79	75.8	32.3	35
	95	75.3	25.0	42

(a) Experiments were performed twice, all doses were tested in triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6 × 10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3 × 10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

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APPENDIX H

CHEMICAL CHARACTERIZATION OF TETRACHLOROETHYLENE

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APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Tetrachloroethylene Performed by the Analytical Chemistry Laboratory

A. Lot no. TA03116F-01

1. Physical properties

	Determined	Literature values
a. Boiling point:	118.8°-119° C (Dupont 900 DTA) 118.8° ± 0.3° C at 733 mm (visual, micro boiling point)	120.97° C at 760 mm (Dreisbach, 1959)
b. Index of refraction:	n_D^{20}:1.5038 ± 0.0003(δ)	n_D^{20}:1.50180 (Eckart, 1923)
c. Density:	d_{22}^{24}:1.6143 ± 0.0002(δ) g/ml	d^{24}:1.613 (Gallant, 1966)
d. Appearance:	Clear colorless liquid	

2. Spectral data

a. Infrared

Instrument:	Beckman IR-12	
Cell:	0.015 and 0.05 mm liquid cell, sodium chloride windows	
Results:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra)

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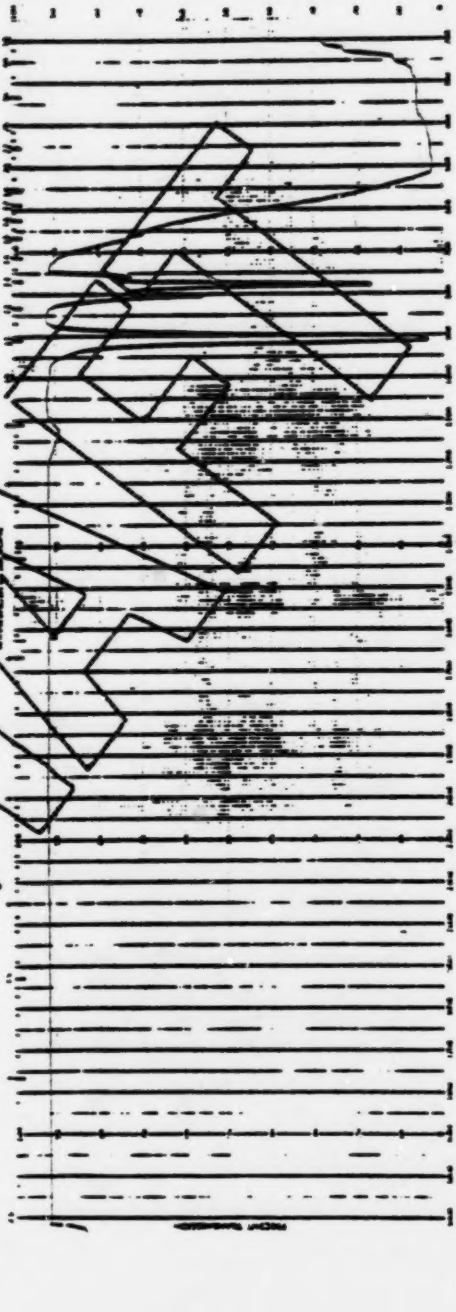

FIGURE 6. INFRARED ABSORPTION SPECTRUM OF TETRACHLOROETHYLENE (LOT NO. TA03116F-01)

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APPENDIX H. CHEMICAL CHARACTERIZATION

		Determined	Literature values
b.	**Ultraviolet/visible**		
	Instrument:	Cary 118	
	Solvent:	Methanol	
	Results:	No absorbance between 350 and 800 nm at a concentration of 1.6 mg/ml. No maximum between 284 and 350 nm but a gradual increase in absorbance toward the solvent cutoff at 284 nm.	No literature reference found. Spectrum consistent with structure.
c.	**Nuclear magnetic resonance**		
	Instrument:	Varian HA-100	
	Solvent:	Neat, tetramethylsilane added	
	Assignments:	No peaks observed	No literature reference found. Consistent with structure.

3. Water analysis (Karl Fischer): 0.0068% ± 0.0009(δ)%

4. Elemental analyses

Element	C	Cl
Theory	14.48	85.52
Determined	14.62 14.48	85.37 85.31

5. Gas chromatography

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 170° C
Detector temperature: 250° C

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a. System 1

Column: GP 20% SP2100/0.1 Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 100° C for 5 minutes; then 100°-170° C at 10° C/minute

Results: Major peak and two impurities

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.6	0.26	0.007
2	1.9	0.84	0.008
3	2.3	1.00	100

b. System 2

Column: 0.2% Carbowax 1500 on 80/100 Carbopack C, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 minutes; then 50°-170° C at 10° C/minute

Results: Major peak and three impurities

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.1	0.09	0.001
2	1.3	0.10	<0.001
3	11.8	0.90	0.004
4	13.1	1.00	100

6. **Conclusions:** The results of the elemental analyses agreed with the theoretical values. Gas chromatography with one system indicated two impurities with areas totaling 0.015% of the major peak. A second system indicated three impurities with areas totaling <0.006% of the major peak. The infrared and nuclear magnetic resonance spectra were consistent with the structure.

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B. Lot no. TA03116F-01--Special bulk purity verification

1. Gas chromatography

Instrument: Varian 3700
Detector: Flame ionization
Column: GP 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 2 mm ID, glass
Inlet temperature: 249° C
Detector temperature: 299° C
Carrier gas: Nitrogen, 32 ml/min
Oven temperature program: 70° C for 5 minutes, then 10° C/minute to 170° C
Sample injected: 5 µl of a neat solution to detect and quantitate impurities; 5 µl of a 1% and 0.5% (v/v) solution to establish detector response linearity

Results: A major peak preceded by two impurities, each with a relative area of 0.003%.

Peak	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.6	0.12	0.003
2	4.0	0.82	0.003
3	4.8	1.00	100

2. Infrared spectroscopy

Instrument: Beckman IR-12
Cell: Silver chloride, 0.025 mm path length

Results: The infrared spectrum (Figure 7) was consistent with a literature spectrum (Sadtler Standard Spectra) and identical to a previously determined spectrum of the same lot.

3. **Conclusions:** The infrared spectrum was consistent with a literature spectrum. Gas chromatography with a GP 20% SP2100/0.1% Carbowax 1500 column, detected a major peak preceded by two impurities each with a relative area of 0.003%. No decrease in the purity of lot no. TA03116F-01 was observed since the original analysis.

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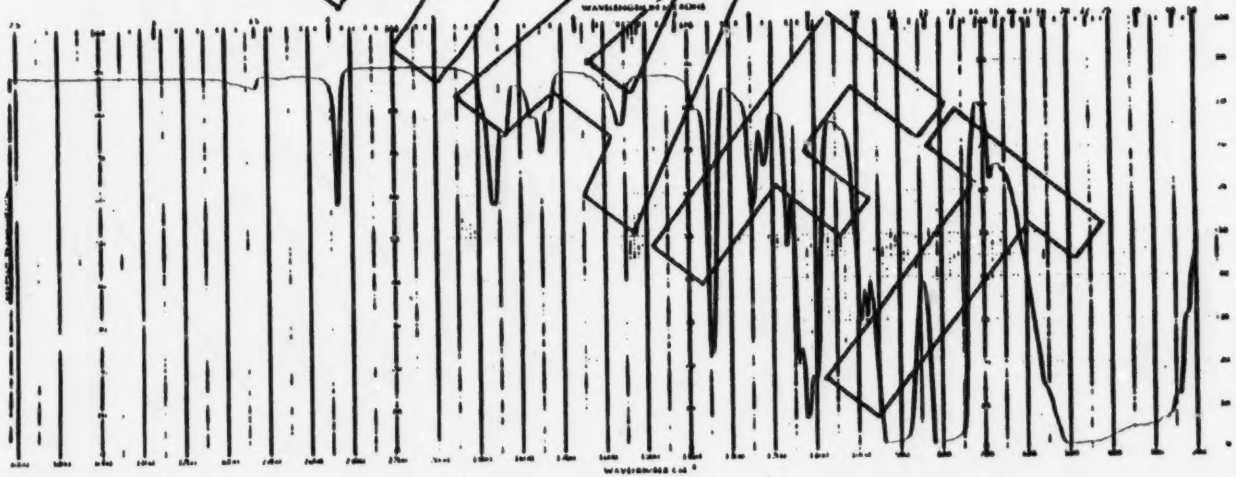

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF TETRACHLOROETHYLENE (LOT NO. TA03116F-01) SPECIAL BULK PURITY VERIFICATION

APPENDIX H. CHEMICAL CHARACTERIZATION

C. Lot no. TA08190D

1. Appearance: Clear colorless liquid

2. Spectral data

	Determined	Literature values
a. Infrared		
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	Methanol	
Results:	No absorbance between 800 and 350 nm at a concentration of 1% (v/v). No maximum from 350 to 215 nm but a gradual increase in absorbance toward 215 nm at a concentration of 0.0001% (v/v).	No literature reference found. Spectrum consistent with structure of tetrachloroethylene.
c. Nuclear magnetic resonance		
Instrument:	Varian EM360-A	
Solvent:	Neat, tetramethylsilane added	
Assignments:	There were no peaks in the spectrum other than the standard peak and side band. The absence of peaks would be expected from a molecule containing no hydrogen atoms.	No literature reference found. Consistent with structure.

3. Water analysis (Karl Fischer): 0.0039% ± 0.0001(δ)%

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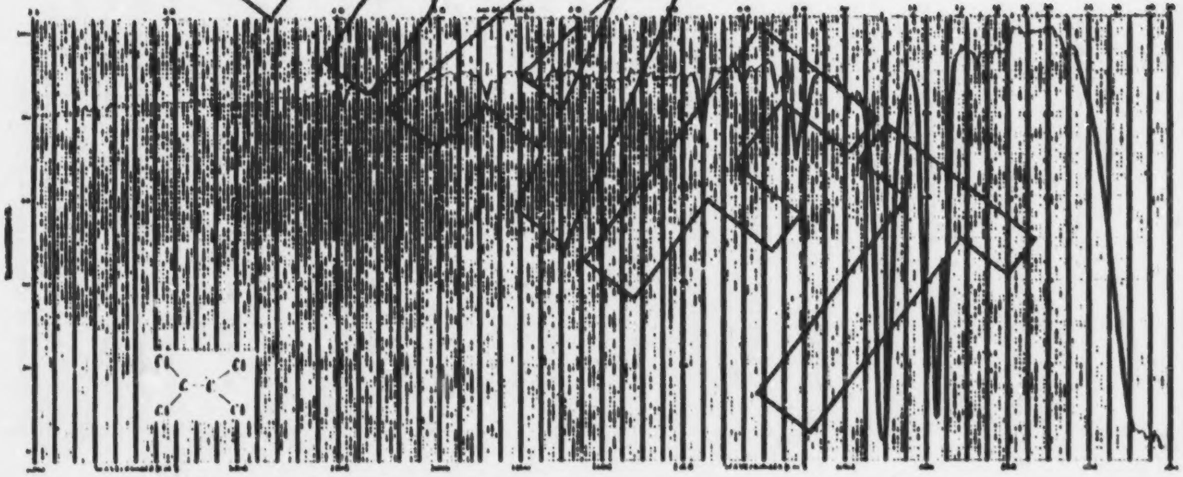

FIGURE 8. INFRARED ABSORPTION SPECTRUM OF TETRACHLOROETHYLENE (LOT NO. TA08190D)

4. **Elemental analyses**

Element	C	Cl
Theory (T)	14.48	85.52
Determined (D)	14.42 14.48	85.55 85.43
Percent D/T	99.79	99.96

5. **Gas chromatography**

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 250° C

a. **System 1**

Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 minutes; then 50°-170° C at 10° C/minute
Carrier gas: Nitrogen, 70 ml/minute
Samples injected: Neat liquid (4 μl) and solution of 1.0% (v/v) tetrachloroethylene in *o*-dichlorobenzene to detect impurities and quantitate the major peak.

Results: Major peak (retention time--9.3 minutes) with no impurities observed with an area ≥ 0.01% of the major peak area. (One impurity was observed before the major peak but had an area < 0.01% of the major peak area.)

b. **System 2**

Oven temperature program: 50° C for 5 minutes; then 50°-200° C at 10° C/minute
Samples injected: Neat liquid (3 μl) and solution of 1.0% (v/v) tetrachloroethylene in *o*-dichlorobenzene to detect impurities and quantitate the major peak.

Results: Major peak (retention time--16.0 minutes) with no impurities observed with an area ≥ 0.01% of the major peak area.

6. **Conclusions:** The results of the elemental analyses for carbon and chlorine were in agreement with the theoretical values. Karl Fischer analysis indicated 0.0039% ± 0.0001(δ)% water. Gas chromatography with two systems indicated only a major peak with no impurities observed having an area ≥0.01% of the major peak. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra are consistent with the structure of tetrachloroethylene.

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II. Test Chemical Stability Study of Lot No. TA03116F-02 Performed by the Analytical Chemistry Laboratory (a)

A. **Sample storage:** Samples of tetrachloroethylene were stored in tightly screw-capped vials for 2 weeks at −20°, 5°, 25°, or 60° C.

B. **Analytical method: Gas chromatography**

Instrument: Bendix 2500 with Hewlett-Packard 3380A automatic integrator
Detector: Flame ionization
Column: Chromosorb 102, 100/120 mesh, glass, 1.8 m × 4 mm ID
Inlet temperature: 250° C
Detector temperature: 255° C
Oven temperature: 230° C
Compound retention time: 6.1 minutes

C. **Results**

Storage Temperature	Relative Average Percent Compound Recovered
−20° C	99.7 ± 5.4
5° C	96.8 ± 5.4
25° C	100.9 ± 5.4
60° C	106.8 ± 5.4

D. **Conclusion:** Tetrachloroethylene is stable when stored for 2 weeks at temperatures up to 60° C.

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(a) This stability study was performed as a part of the characterization of tetrachloroethylene for a gavage study. The results of this study were considered to determine the storage conditions of the bulk chemical in the inhalation studies.

APPENDIX H. CHEMICAL CHARACTERIZATION

III. Test Chemical Stability Study of Lot No. TA08190D Performed by the Testing Laboratory

A. Storage conditions: Bulk chemical, room temperature
Reference chemical, – 20° C

B. Analytical methods

1. Gas chromatography

Instrument: Hewlett-Packard 5830 or 5840A
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.7 m × 4 mm ID, glass
Detector: Flame ionization
Oven temperature: 90° C, isothermal
Carrier gas: Helium
Sample injection: 0.1 µl neat

2. Infrared spectroscopy

Instrument: Beckman Acculab 6 or 8
Cell: Neat liquid between sodium chloride plates

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C. Results

1. Gas chromatography

		Area Percent Purity (a)	
Date	Lot Number	Reference	Bulk Chemical
12/10/80	TA03116F-01	99.99	99.99
01/14/81	TA03116F-01	99.99	99.99
04/23/81	TA03116F-01	99.90	99.89
08/14/81	TA03116F-01	99.99	99.98
12/01/81	TA03116F-01	99.99	99.94
04/14/82	TA08190D	99.96	99.98
08/11/82	TA08190D	99.96	(b) 99.97
12/08/82	TA08190D	99.97	99.98
02/10/83	TA08190D	99.96	99.98

(a) Three determinations were averaged.
(b) Five determinations were averaged.

2. **Infrared spectroscopy:** All bulk chemical spectra were consistent with those of the reference sample that was stored at – 20° C and with spectra supplied by the analytical chemistry laboratory.

D. Conclusion: No significant degradation of the test material occurred during the studies.

APPENDIX I

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS AT BATTELLE PACIFIC NORTHWEST LABORATORIES

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APPENDIX I. GENERATION AND MEASUREMENT

I. Vapor Generation System

The liquid to be vaporized was contained in a 1.6-liter stainless steel reservoir that was housed in a vapor hood within the exposure room. The liquid was pumped from this reservoir to a stainless steel cylinder covered with a glass fiber wick from which the liquid was vaporized (Decker et al., 1982). An 80-watt heater and a temperature-sensing element were incorporated within the cylinder. The heater maintained the vaporizer at 110° ± 2° C. The surface temperature of the vaporizer was slightly less than this temperature. Each cylindrical vaporizer was positioned in the fresh air duct leading directly into the exposure chamber to minimize material loss due to condensation on duct walls (Figure 9).

II. Vapor Concentration Monitoring

A Hewlett-Packard Model 5840 gas chromatograph equipped with a flame ionization detector, a 10% UCW 982 or Chromosorb WAW DMCS 80/100 packed column, and an automatic sampling valve were used to monitor the concentration of tetrachloroethylene in the chambers. All chambers and the room air were sampled approximately twice during each exposure hour. Starting on the 278th exposure day, hexane in nitrogen was added to the sampling sequence to establish instrumental performance. The calibration of the monitoring gas chromatograph was confirmed and corrected as necessary by periodic assay of grab samples from the chambers analyzed on a second gas chromatograph.

Weekly concentrations are graphically presented in Figures 10-13.

III. Vapor Concentration Uniformity in Chamber

Uniformity of vapor concentration in each exposure chamber was measured periodically throughout the study with a portable photoionization detector (Model PI201, HNU Systems, Inc., Newton, MA). The standard deviations of the normalized average concentrations did not exceed ± 7%.

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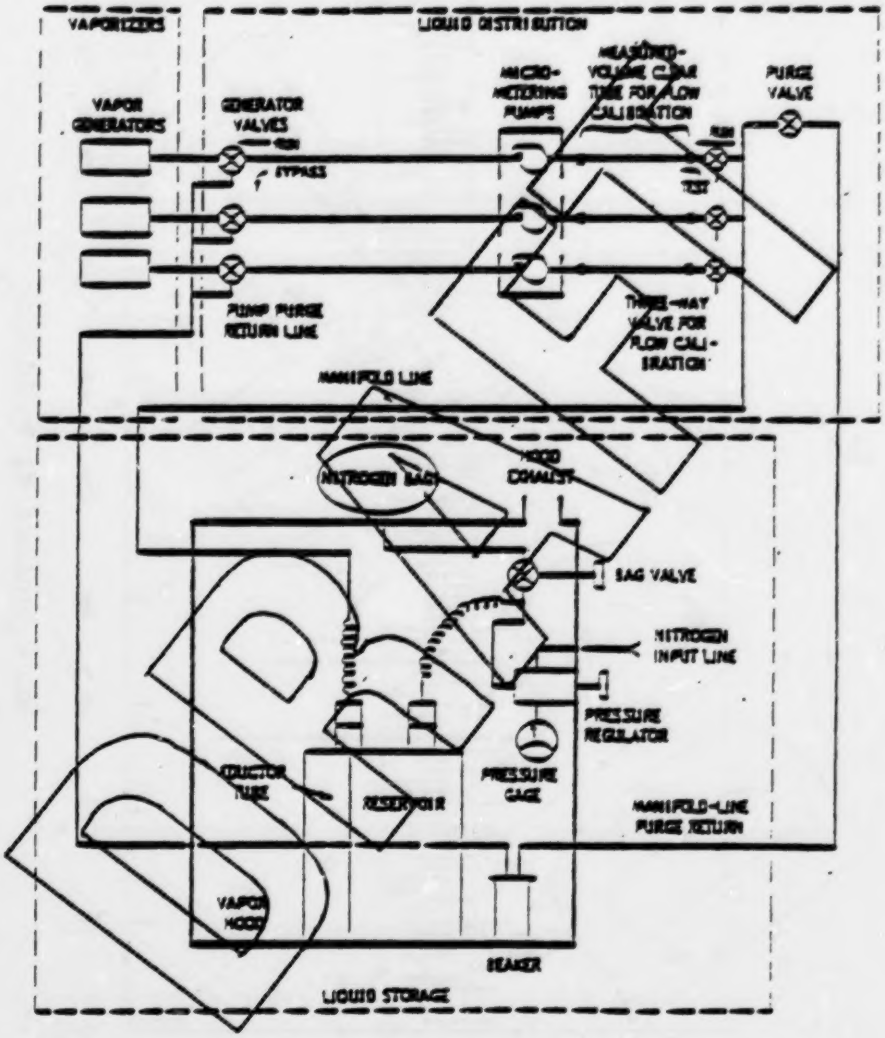
VAPORIZERS
LIQUID DISTRIBUTION
VAPOR GENERATORS
GENERATOR VALVES
RUN
BYPASS
MICRO-METERING PUMPS
MEASURED-VOLUME CLEAR TUBE FOR FLOW CALIBRATION
PURGE VALVE
RUN
TEST
PUMP PURGE RETURN LINE
THREE-WAY VALVE FOR FLOW CALI-BRATION
MANIFOLD LINE
NITROGEN BAG
HOOD EXHAUST
BAG VALVE
NITROGEN INPUT LINE
PRESSURE REGULATOR
EDUCTOR TUBE
RESERVOIR
PRESSURE GAGE
MANIFOLD-LINE PURGE RETURN
VAPOR HOOD
BEAKER
LIQUID STORAGE

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FIGURE 9. TETRACHLOROETHYLENE VAPOR GENERATION SYSTEM

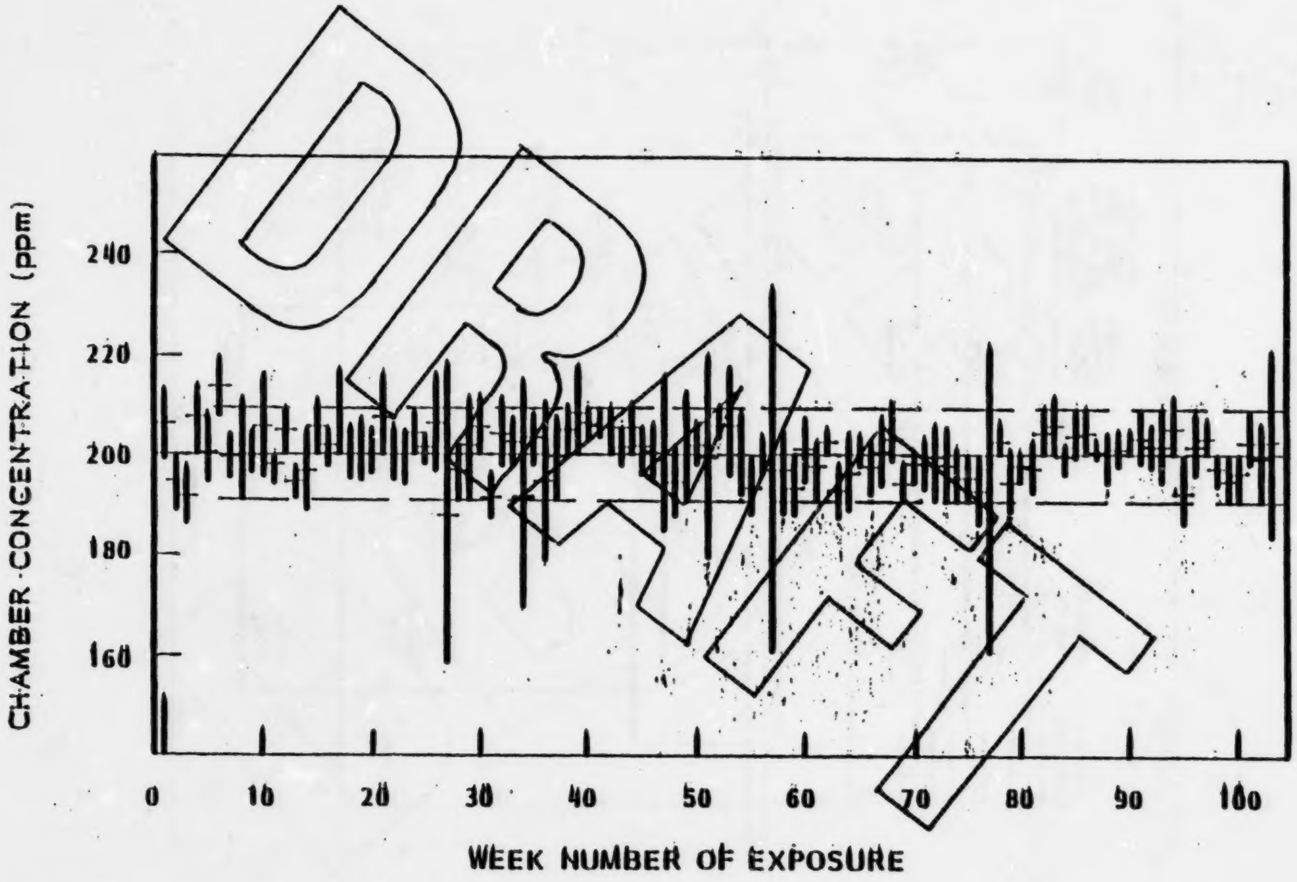

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FIGURE 10. WEEKLY MEAN CONCENTRATION OF TETRACHLOROETHYLENE FOR RATS EXPOSED AT 200 ppm IN THE TWO-YEAR INHALATION STUDIES

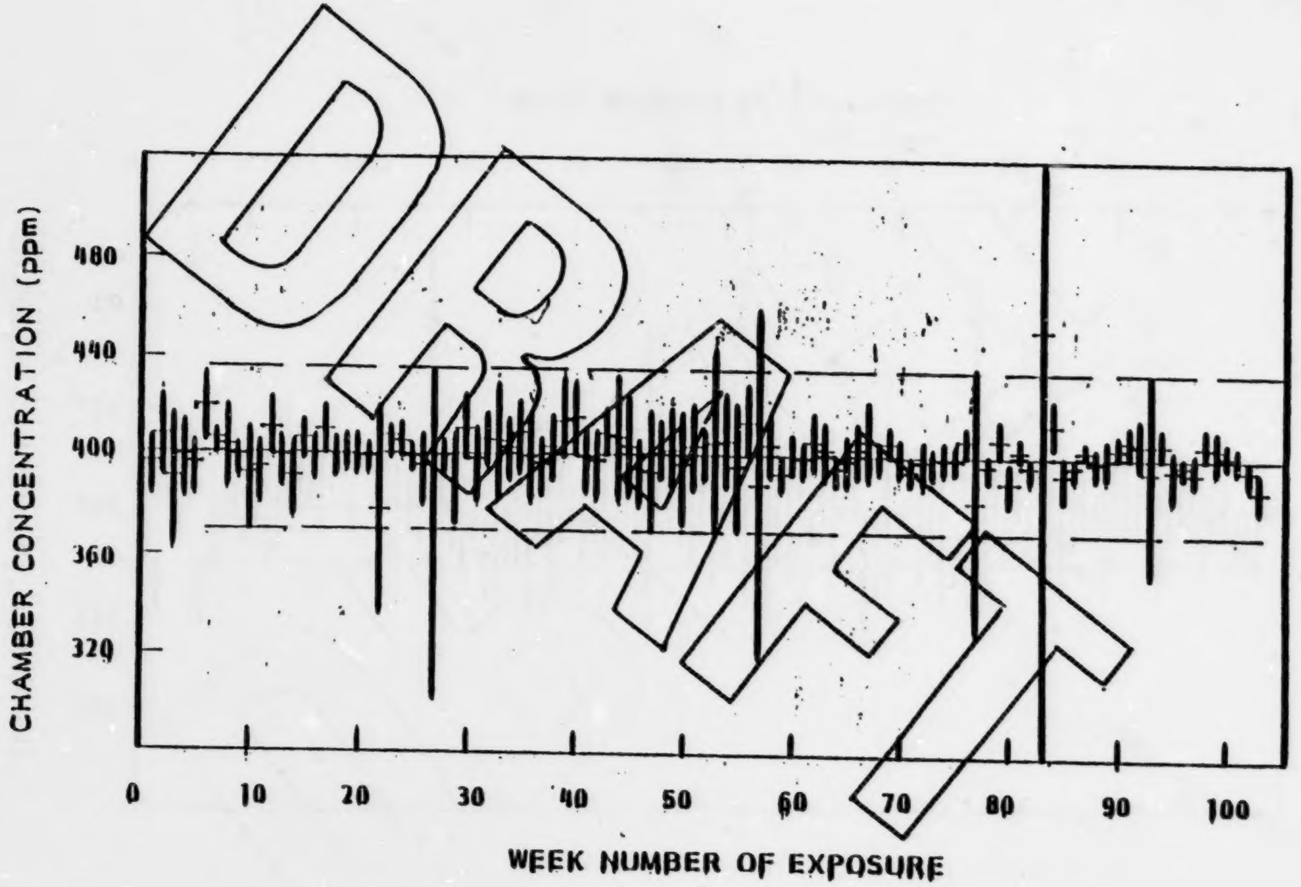

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FIGURE 11. WEEKLY MEAN CONCENTRATION OF TETRACHLOROETHYLENE FOR RATS EXPOSED AT 400 ppm IN THE TWO-YEAR INHALATION STUDIES

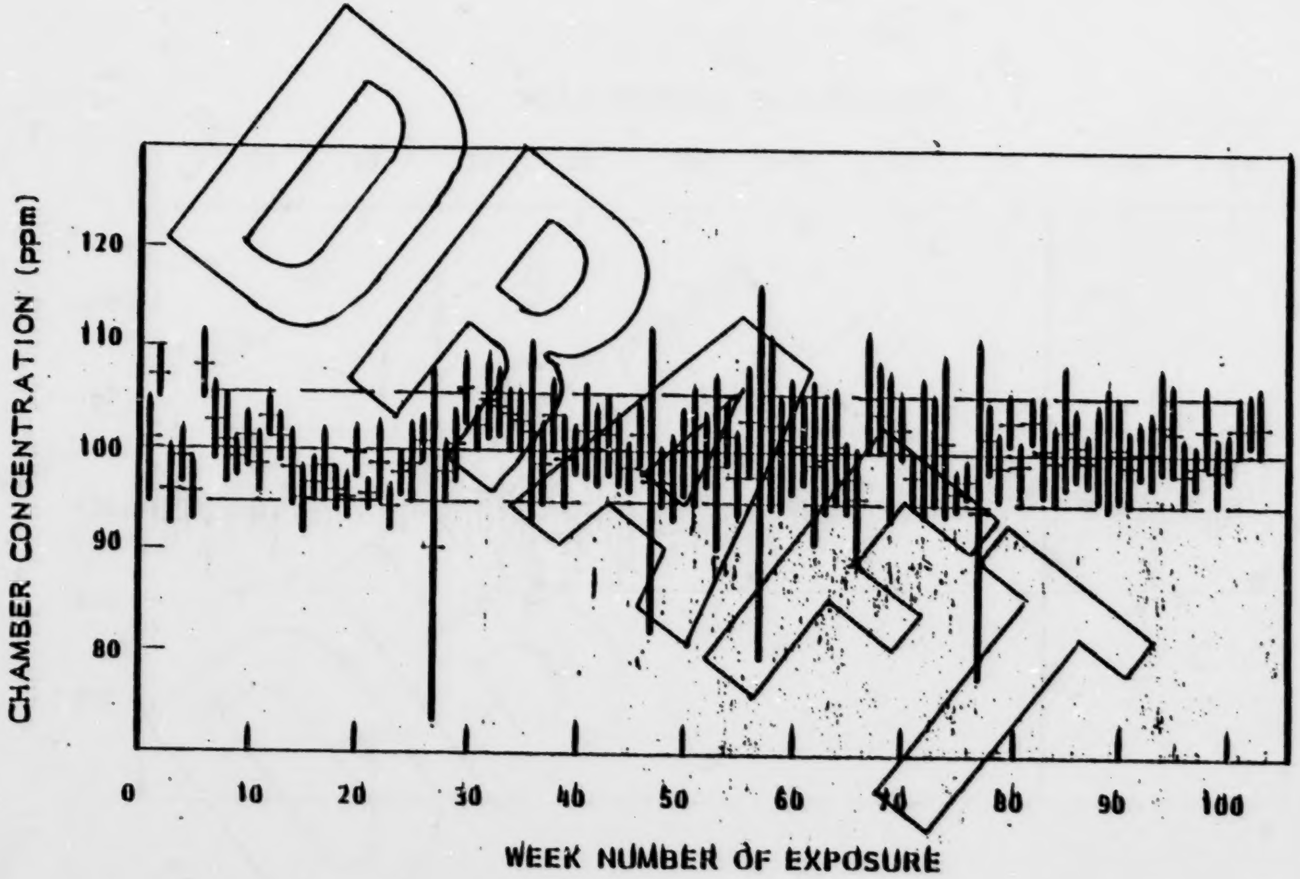

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FIGURE 12. WEEKLY MEAN CONCENTRATION OF TETRACHLOROETHYLENE FOR MICE EXPOSED AT 100 ppm IN THE TWO-YEAR INHALATION STUDIES

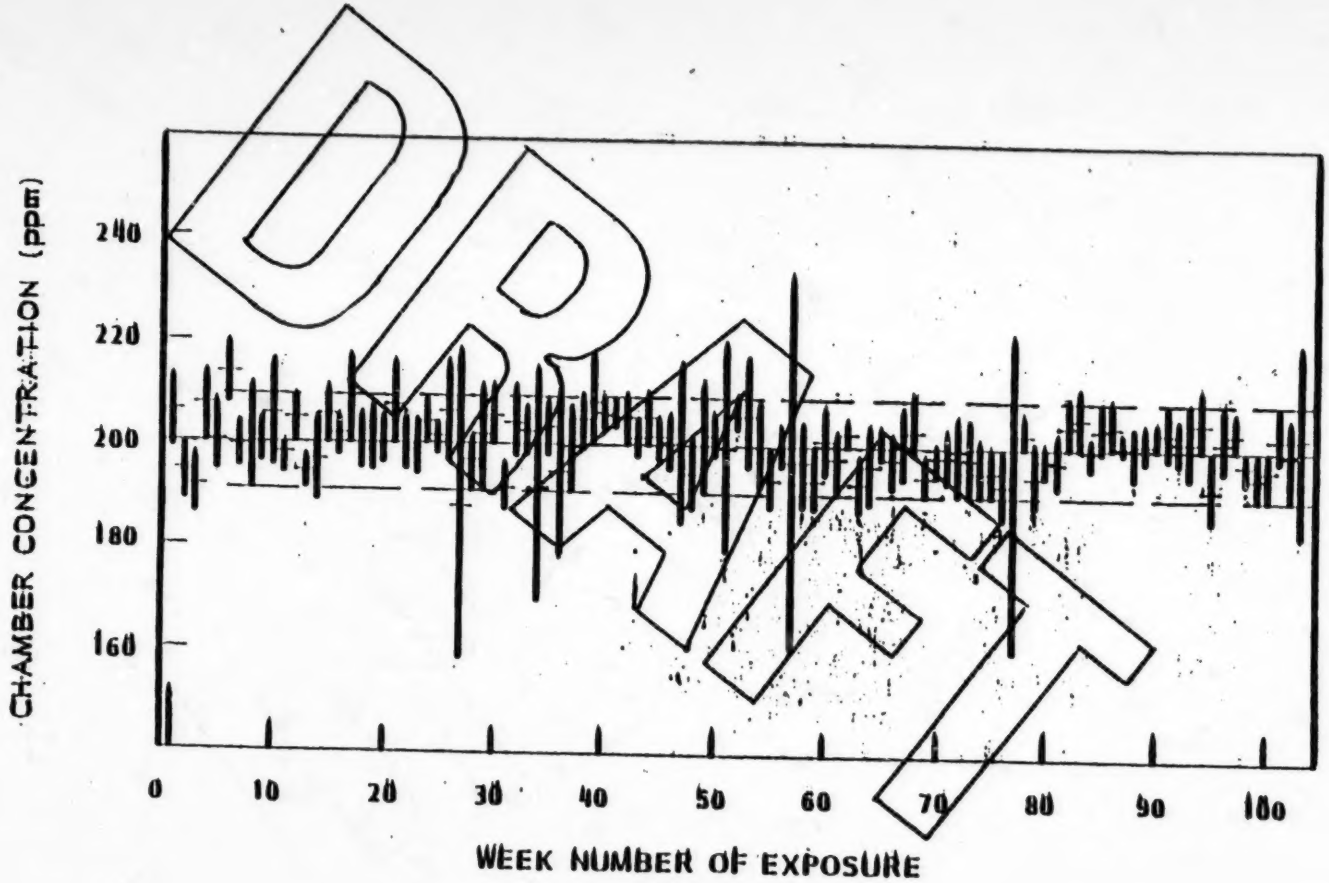

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FIGURE 13. WEEKLY MEAN CONCENTRATION OF TETRACHLOROETHYLENE FOR MICE EXPOSED AT 200 ppm IN THE TWO-YEAR INHALATION STUDIES

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APPENDIX J

RESULTS OF SEROLOGIC ANALYSES

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J. SEROLOGIC ANALYSES

in the Bioassay Program of the National Toxicology Program are produced in n facilities to eliminate potential pathogens that may affect test results.

imals surviving 24 months were collected from 5/50 randomly selected control h sex and species. The blood from each animal was collected and clotted, and the arated. The serum was cooled on ice and shipped to Microbiological Associates' e Animal Diagnostic Service for determination of the antibody titers. The were performed:

glutination ibition	**Complement Fixation**	**ELISA**
eumonia virus of mice)	M.Ad. (mouse adenovirus)	MHV (mouse hepatitis virus)
ovirus type 3)	LCM (lymphocytic choriomeningitis virus	
heiler's lomyelitis virus)		
yoma virus)		
inute virus of mice)		
ectious ectromelia)		
	RCV (rat coronavirus)	
ham rat virus)		
an's H-1 virus)		

sented in Table J1.

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TABLE J1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR INHALATION STUDIES OF TETRACHLOROETHYLENE

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	24	7/10	PVM
		3/10	Sendai
		1/10	RCV
MICE			
	24	3/10	PVM
		3/10	MHV

(a) Blood samples were taken from control animals (5/sex) just before they were killed and sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

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APPENDIX K

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS OF THE NIH 07 DIET

Pelleted Diet: December 1980 to January 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

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TABLE K1. INGREDIENTS OF THE NIH 07 RAT AND MOUSE DIET (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976

(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

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TABLE K2. VITAMINS AND MINERALS IN THE NIH 07 DIET (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D activated animal sterol
K_3	2.8 g	Menadione activity
d-A-tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	d-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	d-biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE K3. NUTRIENT COMPOSITION OF THE NIH 07 DIET (a)

Nutrient	Mean	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
A-tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.8 ± 2.0	14.8-21.0	23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.25 ± 0.15	0.81-1.69	24
Phosphorous (percent)	0.98 ± 0.06	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.

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K4. CONTAMINANT LEVELS OF THE NIH 07 DIET

inant	Mean ± Standard Deviation	Range	Number of Samples
ppm)	0.48 ± 0.17	<0.29-1.06	24
n (ppm) (a)	<0.10		24
m)	1.00 ± 0.74	0.42-3.37	24
(ppm) (b)	< 0.05		24
(ppm)	0.29 ± 0.07	0.13-0.40	24
s (ppb) (a,b)	<10	<5.0-<10.0	24
itrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
itogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
m) (d)	6.68 ± 4.95	<0.4-17.0	24
n) (d)	3.45 ± 2.56	0.9-12.0	24
late count (CFU/g) (e)	40,557 ± 29,431	4,900-88,000	23
late count (CFU/g) (f)	77,617 ± 183,824	4,900-930,000	24
(MPN/g) (g)	16.6 ± 22.9	<3-93	22
(MPN/g) (h)	80.2 ± 236.3	<3-1,100	24
PN/g) (i)	<3		24
osamines (ppb) (j,k)	4.63 ± 4.19	0.8-18.5	21
osamines (ppb) (j,l)	27.15 ± 64.38	0.8-273.2	24
odimethylamine (ppb) (j,k)	3.43 ± 3.96	0.8-16.5	21
odimethylamine (ppb) (j,l)	25.71 ± 64.90	0.8-272	24
opyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
es (ppm)			
BHC (a,m)	<0.01		24
3HC (a)	<0.02		24
a BHC-Lindane (a)	<0.01		24
BHC (a)	<0.01		24
chlor (a)	<0.01		24
(a)	<0.01		24
chlor epoxide (a)	<0.01		24
a)	<0.01		24
a)	<0.01		24
a)	<0.01		24
a)	<0.01		24
(a)	<0.01		24
xychlor (a,n)	<0.05	0.09 (8/26/81)	24
in (a)	<0.01		24
n (a)	<0.01		24
rin (a)	<0.01		24
dane (a)	<0.05		24
hene (a)	<0.1		24
ated PCB's (a)	<0.2		24
l (a)	<0.01		24
(a)	<0.02		24
on (a)	<0.05		24
on (a,n)	<0.1	0.2 (4/27/81)	24
l parathion (a)	<0.02		24
parathion (a)	<0.02		24
hion (o)	0.10 ± 0.07	<0.05-0.27	24
ulfan I (a)	<0.01		24
ulfan II (a)	<0.01		24
ulfan sulfate (a)	<0.03		24

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TABLE K4. CONTAMINANT LEVELS OF THE NIH 07 DIET (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Mean, standard deviation, and range exclude one very high value of 930,000 obtained in the batch produced on 12/22/82.
(f) Mean, standard deviation, and range include the high value listed in footnote c.
(g) Excludes one very high value of 1,100 obtained in the batch produced on 12/16/80 and one high value of 460 obtained in the batch produced on 9/23/82.
(h) Includes the high values listed in footnote e
(i) All values were less than 3 MPN/g (MPN = most probable number).
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote k.
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(o) Thirteen batches contained more than 0.05 ppm.

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APPENDIX L

DATA AUDIT SUMMARY

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APPENDIX L. DATA AUDIT SUMMARY

The experimental data of the NTP Toxicology and Carcinogenesis Studies of Tetrachloroethylene in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies) were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practices requirements. The experiments were conducted between February 1981 and February 1983 at Battelle Pacific Northwest Laboratories, Richland, Washington and were initiated before NTP's requirement of compliance to Good Laboratory Practice standards. The audit was conducted by the Dynamac Corporation (Contract No. N01-ES-38048). The following people were involved in the audit: L. Keifer, Ph.D.; J. Plautz, M.S.; R. Schueler, D.V.M.; M. Perreault, B.S.; C. Sexsmith, B.S.; and E. Zurek. An additional participant was M. Shoaf (Pathology Associates, Inc).

The full report of the audit is on file at the NTP, NIEHS and is available upon request. The audit consisted of an in-depth review of the data and pathology materials collected during the conduct of the study as well as review of the correspondence. For the in-life toxicology data, the review involved examination of 100% of the records on animal receipt and husbandry, mortality, environmental conditions, and dosing, and examination of body weight and clinical observation data for 10% of the animals. In the review of the chemistry data associated with the study, all of the available records concerning receipt, initial analysis, and stability testing by Midwest Research Institute (MRI) were examined. In addition, records pertaining to receipt, bulk chemical analysis, and exposure chamber monitoring gas chromatograph calibration by the testing laboratory were examined. The audit of the pathology materials included review of 100% of the Individual Animal Data Records for gross to microscopic correlation and clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for all control and high dose groups, and verification of the reported pathology on a 10% sample of the animals.

Review of the toxicology data revealed minor discrepancies including: lack of documentation of clinical observations during the early months of the studies, frequent lack of documentation of authorization for moribund kills, poor documentation to differentiate moribund kills from spontaneous deaths, and frequently poor correlations between tissue masses/lesions noted during the in-life portion and at time of necropsy.

A complete review of the available analytical chemistry data revealed that raw chromatographs from MRI analyses were not present. Because of this, it was not possible to verify MRI gas chromatography results. Other records showed that the test material was received and was used to generate exposure atmospheres of 100-, 200-, and 400-ppm target concentrations. Records showed that the bulk chemical was reanalyzed as required. The chemical-use log showed that bulk chemical was regularly withdrawn to refill the vapor generator.

Review of the pathology data revealed that bags of wet tissue were present for all rats and 299/300 mice, and questionable slide/block matches were noted for five mouse slides. Seven instances of undiagnosed potential lesions in target organs of rats were found, and six were adequately resolved. Nine instances of undiagnosed potential tumors in nontarget organs of mice were identified, and all were adequately resolved. Four cases of untrimmed potential tumors in mice were found, and three were resolved without histopathological evaluation. The fourth, a 2-mm liver mass in a control male mouse, was not trimmed because the outcome of the examination would not influence the conclusions of the study.

In summary, the audit revealed no major problem in the conduct of the studies or in collection and documentation of the experimental data. No discrepancies that influenced the final interpretation of the results of these studies were found. The data examined during this audit are considered adequate to support the conclusions presented in the technical report.

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